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ALLERGY

BY

ARTHUR F. COCA, MAX GROLNICK, SAMUEL KARELITZ, ARTHUR P. LOCKE, MILO G. MEYER, LESTER REDDIN, JR., BEATRICE CARRIER SEEGAL, MARION B. SULZBERGER, AND MATTHEW WALZER

Consulting Editor
ARTHUR F. COCA

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EXPERIMENTAL ANAPHYLAXIS IN LOWER ANIMALS

By Beatrice Carrier Seegal

Department of Bacteriology, College of Physicians and Surgeons, Columbia University, New York

Anaphylaxis is a state of induced, specific hypersensitivity. Between 1898 and 1902, Richet[1] introduced the name and initiated the experimental study of this phenomenon. A wealth of information, helpful in the understanding of allergic diseases as well as anaphylaxis, has been accumulated. It is the purpose of this paper to present some of these data, especially those peculiarly pertinent to a monograph on allergy.

The demonstration of anaphylaxis is influenced by a number of variables. Among these are the antigen used for sensitization, the species of animal under investigation, and the method employed to elicit the hypersensitive response. There are three ways in which the hypersensitive response is demonstrable: as anaphylactic shock, as a local inflammatory reaction, or as a widespread inflammatory reaction. The state of anaphylaxis may be achieved passively. When a normal animal is injected with the blood of an anaphylactic animal the recipient also becomes anaphylactic.

Antigen. Different antigens require different quantities for sensitization. Crystalline egg albumin or whole horse serum, when injected parenterally in amounts containing only a few μg., will sensitize the guinea pig so that fatal anaphylactic shock follows the subsequent injection of antigen.[2, 3, 4] Crystalline bovine albumin[5] or crystalline tobacco mosaic virus[6] similarly injected require several milligrams to sensitize and even then fatal shock often does not follow the challenging injection of antigen. When simple chemical substances such as picryl chloride or 2:4 dinitrochlorobenzene are injected repeatedly, intracutaneously in guinea pigs in amounts of 2.5 μg. per injection, typical symptoms of anaphylaxis, and often anaphylactic death, follow the intravenous injection of the specific chemical coupled to a protein.[7] In this latter case it is impossible to know just how much of the injected chemical was responsible for sensitization, since the sensitizing power of such simple chemical substances is probably due to their capacity to combine with protein in the host to form complete antigens.

The physical state in which antigen is administered influences the quantity needed to induce maximum sensitivity. For example, if bovine albumin is precipitated with aluminum hydroxide and this alum precipitate is used to sensitize, the antigen is much more anaphylactogenic than when in solution. A single injection of $\frac{1}{2}$ mg. will render all guinea pigs maximally sensitive.[5] Crystalline ovalbumin, when alum-precipitated, is 4 to nearly 400 times more efficient, depending on the route of administration.[4]

The route by which antigen is given has much to do with the quantity needed to sensitize. Coulson and Stevens[4] present most useful quantitative data. They find, for example, the subcutaneous superior to the intraperitoneal or intravenous route for sensitization of the guinea pig with alum-precipitated ovalbumin. By the former route as little as 0.04 μg. served to sensitize. More than twice this amount was required if the sensitizing

injection was given intraperitoneally, and a sixty-fold increase was necessary for intravenous sensitization. Guinea pigs may be sensitized by routes to which man is exposed, namely, by inhalation or ingestion of antigen.[8] In these circumstances large amounts of antigen are sprayed into the air which the animals breath or are added to their diet.

Doerr and Berger[9] have reported that the incubation period required for sensitivity to develop varies with the antigen. They observed that horse serum albumin required a longer incubation period than the euglobulin fraction. When very small amounts of antigen, of the order of 0.008 mg., were used to sensitize, the incubation period was prolonged for each antigen. An incubation period of 3 or 4 weeks has been used in the recent work[4] designed to determine minimal sensitizing dosages of ovalbumin. However, in the guinea pig at least, the state of sensitivity may persist for months or years.[3]

The quantity of antigen needed to release anaphylactic shock has usually been greater than that required for sensitization. The recent studies of Coulson and Stevens[4] have indicated that this is not necessarily the case. They report on a series of guinea pigs sensitized intra-abdominally with 100 μg. of ovalbumin which were fatally shocked three weeks later by the intravenous injection of 6 μg. of the ovalbumin.

The information so far cited concerning the factor of antigen in sensitization and shock has been obtained from studies in the guinea pig. Other animals are less susceptible to fatal shock and have not been extensively used for experiments in anaphylaxis. Grove[10] has reported studies in the rabbit. She found a series of subcutaneous, intraperitoneal, and intravenous injections of egg white resulted in a high degree of sensitivity in about 75 per cent of the animals. Similarly repeated injections of antigen are usually employed to sensitize other animals, such as the dog and mouse. Rats are peculiarly refractory to anaphylaxis. A table listing methods which have been employed in the sensitization of a number of animal species and the quantity of antigen used to shock is given in Gay.[3]

Anaphylactic Shock. The manifestations of shock vary with the species of animal. It may be recalled that anaphylactic death occurs within 3 to 5 minutes in the guinea pig and is preceded by slow, labored, gasping respirations, cyanosis, prostration, and convulsions. In the rabbit, the cyanosis, prostration, and convulsions occur but the respiratory difficulty is not present. When death ensues, it is also only a matter of minutes. The picture of anaphylactic shock in the dog is that of profound and prolonged prostration, associated with vomiting and bloody diarrhea. Death may be delayed for 1 to 2 hours or slow recovery may take place. Despite the variation in the appearance of the reaction, more careful analysis demonstrates that the symptoms are largely referable to two phenomena, contraction of smooth muscle and an increase in capillary permeability. The location of the smooth muscle, which shows maximum contraction, differs from species to species and hence the picture of shock varies. Increased capillary permeability is more evident in the dog than in the rabbit or guinea pig.

When the guinea pig dead of anaphylaxis is examined at autopsy, the lungs are found fully distended. Microscopic examination of the lungs

provides the explanation. The bronchioles are constricted and the mucous membranes lie in folds, further obstructing the lumen. Inspiration sucks air past this barrier into the alveoli, but the air remains trapped, unable to pass the obstruction upon passive expiration. By the use of radioactive iodine attached to ovalbumin, Dixon and Warren[11] have shown that the antigen in a shocked animal is found in more than twice the expected amount in the edematous, collagenous tissue of the bronchial wall and the adventitia of the pulmonary vessels. Autopsy of the rabbit following anaphylactic death reveals a right auricle and ventricle which are markedly distended, while the inferior vena cava and liver are engorged. In this animal, as shown by Coca,[12] the pulmonary arterioles constrict. The pulmonary blood pressure rises while the systemic blood pressure falls,[13] so that anaphylactic death in this animal also is due to asphyxiation because insufficient blood reaches the lungs.

In the dog, the smooth muscle of the small intestine responds most violently during anaphylactic shock.[14] There is also a marked increase in capillary permeability, as shown by edema and hemorrage in the intestinal mucosa. The liver becomes greatly engorged with blood, a condition which also is probably referable to increased capillary permeability.[15, 16]

Smooth muscle from a sensitized animal, when exposed to antigen *in vitro*, contracts. This phenomenon, the Schultz-Dale reaction,[3] has been shown for both the small intestine and the uterus of the sensitized guinea pig. Grove[17] has demonstrated similar contraction of arterial smooth muscle from this animal. Sollmann and Gilbert[18, 18a] have studied the contraction of the bronchioles and the pulmonary arterioles of the rabbit lung. Thin sections of lung from sensitized animals, placed in Ringer-Locke solution and observed under the microscope, show visible contraction of both tissues upon the addition of the specific antigen.

A knowledge of the relation of anaphylaxis to antibody titer is of fundamental importance to the understanding of the mechanism of anaphylactic shock. The guinea pig may be fatally shocked in the absence of circulating antibodies, demonstrable by any *in vitro* test. Kabat and his associates,[2] during their studies of passive anaphylaxis, have shown the reason for this. The guinea pig may be *passively* sensitized with such a small amount of antibody that its presence cannot be demonstrated except by the highly sensitive biological method of anaphylactic shock. This work will be described later. Jackson[19] has attempted to determine the quantity of circulating antibody which is required to insure anaphylactic shock in the actively sensitized rabbit. She found that a high titer of circulating antibody does not guarantee death from anaphylaxis in the rabbit. However, all animals which succumbed to anaphylactic shock had at least 3.56 mg. of antibody protein per cc. of serum.

Local Inflammatory Reaction. When the test for anaphylactic sensitivity is made by the local injection of the specific antigen, a quite different type of hypersensitive reaction is obtained. The first experiments of this kind were those of Arthus, who gave rabbits repeated subcutaneous injections of horse serum. No reaction resulted following the first few injections. The

later injections, however, induced erythema and edema which developed over a period of hours. In some cases the local inflammatory response was so severe that necrosis and sloughing occurred in the course of a day or two. Microscopically the reaction begins almost immediately. The change in the status of the capillary wall has been subjected to direct observation by Abell and Schenck.[20] They followed the result of introducing horse serum into the moat of an ear chamber in rabbits sensitive to this antigen. Contraction of arterioles, slowing of the circulation, migration of leucocytes through the vessel wall, and clumping of the red cells were recorded. Gerlach[21] has compared the histological picture of the reaction in several species of animals and in man at varying time intervals following the injection of the antigen. The histopathology of this reaction is not distinctive from that of acute inflammation due to other causes.[22]

In the sensitized rabbit, the Arthus reaction may be elicited in all tissues so far investigated. If the reaction takes place in a vital organ, physiological disturbances result. For example, inhalation of an antigen by a sensitive animal may produce congestion of the lungs with the histological appearance of acute pneumonia.[23] The introduction of specific antigen into the pericardial cavity results in an acute pericarditis and myocarditis, which may be so severe as to cause death from cardiac failure.[24] Similarly, the introduction of antigen into the brain of a hypersensitive animal produces profound inflammation that is manifested by neuromuscular disturbances.[25]

It is possible to reverse the usual order in demonstrating local hypersensitivity, namely, to induce local sensitization by local application of the antigen and subsequently to elicit evidence of this by intravenous administration of the antigen. Such a reaction has been carried out in the rabbit eye.[26] If a foreign protein is placed in the anterior chamber of the rabbit eye, after two to three weeks the intravenous injection of the same antigen results in hyperemia of the iris and conjunctiva, edema of the conjunctiva, and lacrimation, all limited to the previously sensitized eye. This reaction develops about two hours following the shocking injection, reaches a maximum in five hours, and usually subsides within 24 hours. Parenteral injection of antigen is not necessary to elicit the reaction, since it was obtained in 11 of 38 animals in which the shocking dose of antigen was given in large amounts by stomach tube.

Such a locally sensitized eye may be kept continuously inflamed over a period of days if several antigens have been injected simultaneously into the anterior chamber for sensitization. Some weeks later each antigen in turn is injected intravenously on succeeding days. The inflammatory response may be obtained to each successive antigen.[26]

Desensitization follows the injection of the specific antigen, but is temporary. The eye may become inflamed upon subsequent tests with the same antigen after a suitable period of time. The mechanism for this return of sensitization may perhaps be found in a series of experiments designed to test the effect of non-specific inflammation upon the capacity of the eye to become sensitive to a circulating antigen.[27] A series of rabbits was divided into three groups: group one was injected with glycerin into

the anterior chamber of the right eye and, during the period of inflammation which followed, egg white was injected intravenously; group two received only the glycerin in the eye; and group three only the egg white, intravenously. Four weeks later all animals were injected intravenously with egg white. There was no reaction in groups two or three to this treatment, but in 12 of 21 animals belonging to group one a typical local inflammatory reaction in the glycerin-treated eye occurred. This experiment is interpreted to indicate that the circulating antigen is localized in the non-specifically inflamed eye and here serves to produce an area of local sensitization, which is demonstrated after a suitable incubation period by the intravenous injection of the specific allergen. An allergic inflammation should be highly efficacious for concentrating antigen, since the antigen is drawn to the area, first, by the specific antibody and, secondly, by the inflammation. Thus, new antigen is available for renewal of sensitization of the local area.

The eye is not the only organ which has been locally sensitized. It has been found that the rabbit heart may similarly exhibit local sensitization after antigen is injected directly into the pericardial cavity.[28] Rabbits were injected with 1 cc. of egg white into the pericardial cavity, while controls received the same antigen intraperitoneally or intravenously. Four to 7 weeks after the sensitizing injection the animals were sacrificed and heart preparations from each group were prepared according to the method of Wilcox and Andrus.[29] These organs were perfused with Ringer-Locke solution and the effect upon coronary flow of the addition of egg white was measured graphically. Fourteen of the 15 hearts from animals sensitized intrapericardially showed the typical anaphylactic reaction characterized by a drop of 22 to 64 per cent in the rate of flow of the perfusate through the coronary vessels. Only 7 of the 31 hearts taken from the other animals sensitized intraperitoneally or intravenously gave a positive reaction by showing a decrease in rate of coronary flow of 15 to 45 per cent. In short, the direct exposure of the heart to 1 cc. of antigen sensitized it, whereas a similar amount of antigen injected elsewhere was usually insufficient to sensitize the heart.

General Inflammatory Response. The third group of reactions which we are considering under experimental anaphylaxis are those which follow a single, large intravenous injection, or closely spaced multiple injections, of a foreign protein. "Serum sickness" has been produced experimentally in rabbits by Fleisher and Jones.[30] In these animals it is characterized by erythema and edema of the ears, which develops 3 to 8 days following intravenous injection of 5–10 cc. per kilogram of horse serum. Khorazo[31] observed the reaction following the injection of horse serum but failed to obtain the reaction when human, sheep, guinea pig, or dog serum was employed. We[5] have observed one typical serum sickness reaction in the ears of a rabbit 44 days following the intravenous injection of 1 gm. of crystalline bovine albumin. Three other animals had unilateral reactions which occurred in 20 to 30 days in the ear receiving the intravenous injection.

Rich has again focused attention on perivascular inflammation which can be found in rabbits following massive injections of antigen. Klinge[32]

described such lesions and has reviewed the earlier work. Rich and Gregory[33] have produced diffuse periarteritis nodosa by the same technique used to induce serum sickness in rabbits. A single large injection of horse serum given intravenously may result in about three weeks in widely scattered periarterial collections of leucocytes, which may invade to the intima and which are associated with fibrinoid and hyaline alterations and necrosis of the walls, producing the histopathological picture of periarteritis nodosa. These workers[34] also found cardiac lesions which, in their basic characteristics, resemble closely those of rheumatic carditis.

More recent observations of this type of anaphylactic reaction are those of Hawn and Janeway,[35] who worked with two single antigens, crystalline bovine albumin and a highly purified bovine gamma globulin. These two proteins derived from the same animal species gave rise to somewhat different diseases when injected intravenously in rabbits. The albumin disappeared more slowly from the circulation and appeared to be a poor antigen, but in those animals in which lesions were found, after a period of two to three weeks, they were distributed throughout the arterial system and mimicked those of periarteritis nodosa. On the other hand, the rabbits injected with gamma globulin developed lesions more rapidly and lost the foreign protein from the circulation more rapidly than in the case of rabbits given the albumin. The lesions, instead of being distributed throughout the arterial system, were predominantly in the myocardium and glomeruli of the kidney.

Ehrich, Seifter, and Forman[36] have examined the pathologic changes resulting from the injection of varying amounts of horse or duck serum in rabbits which were sacrificed 3 to 34 days later. Allergic arteritis, marked glomerulonephritis, myocardial necrosis, and Aschoff-like bodies in the myocardium are described. Moore and his associates[37] have been successful in producing acute rheumatic-like heart lesions in mice by the repeated parenteral injection of egg white. More *et al.*[38, 39] have utilized bovine serum gamma globulin as well as horse serum in their studies on allergic serum disease. The horse serum produced diffuse arteritis and the bovine gamma globulin both glomerulonephritis and granulomatous lesions of the heart valves as well as an arteritis. A useful review of the literature is to be found in reference 38.

No account of the diffuse inflammatory reactions of hypersensitivity should fail to include mention of the lesions which have been produced by the injection of homologous and autogenous antigens. The Caveltis[40] have reported that the injection of rats with homologous rat kidney, mixed with killed (δ) hemolytic streptococci, produces a chronic progressive nephritis in these animals. Kabat, Wolf, and Bezer[41] and Morgan[42] have produced an acute disseminated encephalomyelitis, resembling multiple sclerosis, by injecting monkeys intramuscularly with heterologous or homologous suspensions of brain or spinal cord. These antigens were mixed with killed tubercle bacilli and suspended in oil previous to injection, according to the adjuvant technique of Freund and McDermott,[43] which serves to enhance antibody production. Kabat has shown that injection of a monkey with a portion of

its own cortex, removed surgically, serves as well to induce the lesions.[44] Hydrolized, autogenous rabbit serum or saline extract of the rabbit's skin have been used by Gosset, Jahiel, and Delaunays[45] and Jahiel and Jahiel[45A] to sensitize the rabbit's own lung. A month after the initial injection of 0.5 cc. into the lung parenchyma an intravenous injection of the same material produces an acute pneumonitis of the previously sensitized lung.

Passive Sensitization. The serum of an anaphylactic animal may be capable of passively sensitizing a normal animal. This was first demonstrated by injecting a normal guinea pig with the serum of a sensitized guinea pig.[3] Four hours later the injection of the specific antigen elicited anaphylactic shock. Antibody-containing serums from the rabbit, as well as from the goat and man, have also been found capable of passively sensitizing the guinea pig to anaphylactic shock, whereas antiserums from the rat, the horse, the chicken and from cattle have failed to accomplish this passive sensitization. On the other hand, horse antipneumococcus serum has passively sensitized the guinea pig so that an immediate wheal and erythema skin reaction,[46] or an Arthus-like reaction,[47] follows the intracutaneous injection of the carbohydrate antigen. Likewise, horse antipneumococcus serum transfers the Arthus type of hypersensitivity to the rabbit[48] and the anaphylactic type of hypersensitivity to the dog.[49] It is thus apparent that passive transfer of hypersensitivity is conditioned by the donor and recipient hosts and by the nature of the test employed to demonstrate the hypersensitive state.

Quantitative studies in passive sensitization of the guinea pig and rabbit, utilizing sera of chemically defined antibody titer, have yielded most interesting data concerning the amount of antibody necessary to accomplish sensitization. Kabat and his associates[50] have shown that only 0.03 mg. of anti-crystalline egg albumin antibody N or antipneumococcus type III antibody N is sufficient, when injected intravenously, to render a 250 gm. guinea pig susceptible to lethal anaphylactic shock, when challenged with the specific antigen 48 hours later. Three one-hundredths of a milligram of antibody nitrogen, when distributed throughout the circulation and body tissues, is not detectable by *in vitro* methods. Indeed, when five times this amount of anti-egg albumin N was injected it still could not be demonstrated 48 hours following injection. This indicates that the biological test of anaphylaxis is better able to detect antibody than the presently available test-tube tests. Another striking illustration of this is furnished by the observation that the excised uterus from a guinea pig sensitized passively with 0.03 mg. of anti-egg albumin N will show the typical Schultz-Dale reaction. The addition of 1 mg. of antigen to the bath containing the uterine strip causes contraction. Kabat and Landow[51] have calculated that the uterus probably contains amounts of antibody N of the order of 0.01 μg.

Fischel and Kabat[52] and Benacerraf and Kabat[47] have obtained data on the quantitative relation between antigen and antibody in the passively induced Arthus reaction. As in anaphylactic shock, small quantities of antibody sufficed to induce sensitivity. If the sensitizing injection was

given intracutaneously, 0.025 mg. of antibody N sensitized the rabbit locally, and 0.09 mg. the guinea pig.

The quantitative studies on anaphylaxis in Kabat's laboratory have disclosed a very interesting role which the nature of the antibody plays in passively induced anaphylactic shock and the Arthus reaction. If nonprecipitable or "univalent" rabbit antiovalbumin was utilized passively to sensitize the guinea pig to anaphylactic shock, 0.03 mg. of this antibody was required. The non-precipitating antibody was as efficient as the precipitating antibody.[53] On the contrary, equivalent weights of nonprecipitable antibody were unable to prepare the animals for a passive Arthus reaction.[47]

The time which must elapse between the injection of antibody and the development of hypersensitivity in the passively sensitized animal is a factor both of the animal species and of the quantity of antigen. The rabbit becomes sensitive immediately after injection of the homologous antiserum,[54] as do the dog and mouse. In the rabbit, passive sensitivity is rapidly lost, but may last 20 days in the dog.[15] It has been concluded from most of the observations in guinea pigs that an incubation period of two hours or more following the injection of the antiserum is necessary to accomplish passive sensitization. This statement is at variance with some of the reported data.[16] Benacerraf and Kabat[55] have carried out quantitative studies concerning the relation of the amount of sensitizing antibody to the minimum latent period before anaphylactic shock is demonstrable. When the sensitizing dose of 0.03 mg. antiovalbumin N is increased approximately 30 times, animals may be fatally shocked when antigen is injected immediately after the antiserum. A fourteen-fold increase in antibody resulted in fatal shock one-half hour later. As these authors state, a reaction of some kind takes place as the interval between sensitization and shock is lengthened, which increases the efficiency of a given quantity of antibody in effecting sensitization.

Discussion. Allergic diseases of man were among the diseases of unknown etiology until experimental observations in animals discovered the methods to establish the state of anaphylaxis or hypersensitivity. The fact that *repeated* exposure of an animal to an *initially* harmless substance might induce a serious or even fatal reaction was then found to have its counterpart in human experience. Once it was accepted that acquired hypersensitivity to agents in our environment might cause a variety of diseases, such as hay fever, asthma, or urticaria, the list of possible allergic diseases of man grew rapidly. Soon the many manifestations of known allergic diseases and of suspected allergic diseases outstripped the experimentally induced hypersensitivities. Because many manifestations of allergic diseases in man failed to find a suitable counterpart in experimental work in animals, the question has arisen in the minds of many as to whether certain of the allergic diseases of man are unique to him. It would seem, as further experimental work develops, that man and his allergies are not unique.

The experiments reviewed here have been selected with a view to pre-

senting some of the means of experimental sensitization which may also operate in human allergies. The varieties of the manifestations of experimental anaphylaxis have been described with the purpose of bringing out similarities between these diseases and the natural allergic diseases of man.

No attempt has been made to discuss the most important question of the relation of the reagins or passively sensitizing antibodies found in allergic diseases to those antibodies which operate in the passive sensitization of animals. This is a very crucial field of investigation, which is only just beginning to unfold and which would require a separate paper to present.

A few of the experiments discussed in the text are summarized for the purpose of re-emphasizing their interest to the allergist.

(1) Minute amounts of antigen, even less that 1 μg, may suffice to sensitize an animal, and only slightly larger amounts can produce shock. Such small quantities of antigen are well within the range to which man is naturally exposed.

(2) Sensitization of a local area of the body can be established if antigen is concentrated in this area. One condition under which such concentration can occur is found if antigen is circulating at a time when a local focus of inflammation is present in the body. Circulating antigen may be concentrated in this local area.

(3) The amount of antibody necessary to establish hypersensitivity may be so small that *in vitro* methods cannot demonstrate its presence in the circulation. The *in vivo* tests for hypersensitivity are much more sensitive than the *in vitro* tests.

(4) Both sensitization and shock can be experimentally elicited by ingestion or inhalation of antigen as well as by parenteral administration.

(5) The local and systemic effects of hypersensitivity may be profoundly damaging and simulate such chronic diseases in man as periarteritis nodosa, nephritis, and multiple sclerosis, as well as heart lesions not unlike those of rheumatic fever.

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A CLASSIFICATION OF ALLERGIC DISEASES AND THEIR SPECIFIC MANIFESTATIONS IN ANIMALS

By Lester Reddin, Jr.
*Merck and Company, Westfield, New Jersey**

Hypersensitivity

In order that we may consider adequately the identity of certain manifestations of the allergic reaction as appearing in animals, it would be well, first of all, to develop a suitable working classification of this group of disturbances and its relationship to other physiologic phenomena.

So much has already been entered in the annals of modern medicine on the historical aspects of the field that only the salient points necessary to establish our logic in placing each of the subdivisions in its proper category need be mentioned here. Among the controversial issues in our medical concepts of today is that of the relationship of one manifestation of specific sensitivity to another. As in other fields where the thinking is healthy and progressive, these issues are vigorously expressed and as firmly held.

Our early knowledge of sensitivity did not allow us to speculate as to the mechanism of the reaction. It was in 1902 that Richet and Portier [47b] gave the name "anaphylaxis" to a peculiar finding in their experimental dogs. They observed that dogs which had survived previous injections of extracts of certain actinians would suffer on subsequent injections, with a syndrome of characteristic symptoms, and would rapidly succumb. They had expected that the previous injection would produce a state of resistance rather than an increase in susceptibility. It was this lack of resistance that caused them to coin the term "anaphylaxis": without protection.

The modern concept of this altered state can be based on the report of von Pirquet and Schick[40] on serum sickness. Although this report did not, at the time, prove the antigen-antibody interreaction as the etiologic factor, these workers are to be credited with postulating its existence before the mechanism of anaphylaxis of animals had been worked out. The dependence of anaphylaxis on antibody was demonstrated by Otto[39] and by Friedemann[21] in the guinea pig, by Richet[47a] in the dog, and by Nicolle[38] in the rabbit by injecting the serum from a sensitized animal into a normal one and showing the latter, on the following day, to be hypersensitive to the homologous antigen.

The existence of the hypersensitive state in the human being had long been known or suspected, but it was not until 1921 that evidence was presented to establish the antigen-antibody mediation of the phenomenon. It was in this year that Prausnitz and Küstner[41] published the results of their brilliant observations of the passive transfer of sensitivity to non-sensitive subjects by way of the serum.

Thus, the establishment of the antigen-antibody relationship of these conditions, *i.e.*, anaphylaxis of animals and allergic diseases of man, prompted Coca[12] to consider these two diseases in relation to the field of

* Present address: Lawrence Veterinary Hospital, Verona, New Jersey.

immunology as a whole. His classification, with some extension, may be illustrated by TABLE 1.

It is from a casual standpoint only that we are interested at the moment with the top of this table, and then only in order to orient our thinking. It is, on the other hand, with the subdivision of the group of immunological diseases, hypersensitiveness, that we will deal (See TABLE 2).

Hypersensitivity has been defined by Coca[10] as follows: "If an individual reacts specifically with characteristic symptoms to the administration of, or to contact with, a quantity of any substance, which, to the majority of

TABLE 1

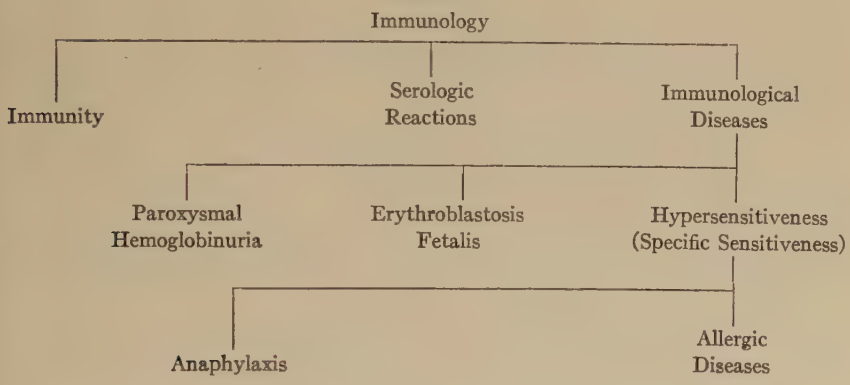

TABLE 2

Specific Sensitiveness	
A. Anaphylaxis	B. Allergic diseases 1. Atopy-reaginic allergy 2. Contact dermatitis 3. Serum sickness 4. Drug allergy 5. Hypersensitiveness of infection 6. Non-atopic or non-reaginic allergy

the members of the same species of animal that have not had previous contact with it is innocuous, that individual is said to be hypersensitive to that substance."

It is unfortunate, from an etymological point of view, that the term "hypersensitive" should have received such wide usage, since it denotes an increased state of sensitivity, thereby implying that all individuals are sensitive to some degree. It would, on the other hand, seem better to adopt the term "specific sensitiveness" as suggested by Coca.[10]

Anaphylaxis

For years, in many circles, the words "anaphylaxis" and "allergy" have been used synonymously. This interchangeable usage, however, has not

been borne out by experimental and clinical evidence. Anaphylaxis can best be described as a state of specific sensitivity of animals, induced either by previous contact with the antigen or passively with specific antibodies for it from another individual and mediated by the presence, in certain tissues, of anaphylactic antibodies. These antibodies are precipitins. They have the capacity of sensitizing smooth muscle and can be classically demonstrated by the Dale method of contraction of the isolated uterine strip.

That these antibodies are not the same as those found in atopy and other manifestations of allergic diseases of man and animals will be shown in the discussion under these other headings.

Allergic Diseases

Atopy. In its earliest definition, atopy encompassed "certain clinical forms of human hypersensitiveness that do not occur, so far as is known, in the lower animal and which are subject to an hereditary influence."[16] Later developments have changed our views somewhat to establish its existence in lower animals and its mediation by the sensitizing antibody reagin.

Subsequent to the suggestion of Wolff-Eisner,[58] and later Meltzer,[37] that hay fever was an expression of hypersensitiveness, many unsuccessful attempts were made to transfer an antibody to the guinea pig by way of the serum of the sensitive individual. These efforts were directed toward the duplication in the guinea pig of the classical anaphylactic syndrome.

As mentioned earlier, an antigen-antibody concept of the mechanism of hay fever was suspected. This theory was given further credibility by the development of the technique of skin testing for hypersensitivity to inhalants. It was not until 1921, however, that the presence of antibody of the specifically sensitive individual was shown. In that year, Prausnitz and Küstner[41] succeeded in passively inducing a state of local sensitivity in the normal human skin following the injection of serum from a sensitive subject. Specific antibodies were later characterized in atopic sera and given the name "atopic reagin" by Grove and Coca.[25] Conditions in the human subject characterized by the presence of these sensitizing antibodies (*i.e.*, reagins) are, for example, certain forms of asthma, hay fever, and eczema. The identity of the mechanism of anaphylaxis of animals and asthma of humans was theorized by many, but consistent experimental proof failed to be developed to warrant any such similarity.

In order to discuss further the difference in the two phenomena, reference can well be made here to a comparison of the two types of antibodies to a single antigen (TABLE 3). Although these various points of differentiation have been open to criticism by many workers, the bulk of information recorded will be seen to bear out their accuracy. Because of the many published examples of this positive proof, only a few will be cited here.

Studying the sensitizing properties of a serum from an atopic subject, Donnally[19] showed that it was capable of sensitizing human skin in quantities as small as $\frac{1}{3200}$ cc., whereas Coca and Grove[15] have cited the consistent failure of the anaphylactic antibodies to sensitize human skin in any

concentration. The permanent attachment of the atopic reagins to the body cells at the site of injection has been demonstrated by Coca and Grove,[15] who have shown that this attachment can be observed for at least four weeks. This is in contrast to the rapid diffusibility of anaphylactic antibodies from their site of injection. It has been shown that this will occur in the rabbit within eighteen hours after injection. Using the technique of Dale, it has been consistently shown that anaphylactic antibodies are capable of passively sensitizing guinea pig uterine strips, while Prausnitz and Küstner,[41] Cooke, Flood, and Coca,[17] and Coca and Grove[15] were never able to accomplish this, using human atopic serum.

DeBesche[2] has shown that, although precipitins may on occasion be found to be present in the sera of atopic individuals, these antibodies fluctuate above and below the level at which they are demonstrable *in vitro*. Cooke, Flood, and Coca have further pointed out that the presence of these antibodies in human serum can in no way be demonstrated by passive transfer to the guinea pig, even by the very delicate technique of Dale, while, at the same time, Grove[24] has demonstrated that rabbits whose serum showed satisfactory precipitin titers would invariable die in anaphylactic shock when egg white was injected intravenously immediately after the blood titrations had been made.

Table 3

Atopic reagins	*Anaphylactic antibodies*
1. Sensitize human skin in as little as $\frac{1}{32000}$ cc.	1. Do not sensitize human skin in any quantity.
2. Are quickly and permanently attached to body cells.	2. Are diffused throughout body from injection.
3. Do not sensitize guinea pigs.	3. Sensitize guinea pigs.
4. Are not precipitating antibodies.	4. Are precipitating antibodies.
5. Typically do not inactivate antigen.	5. Inactivate the antigen.
6. Are susceptible to heat (destroyed at 56°C. for ½ hour).	6. Only slightly affected by ½ hour at 56°C. heat.

Another criterion in the differentiation of these two antibodies was established by Levine and Coca[35] and confirmed by Jadassohn.[28] These investigators have shown that, while the atopic excitant is capable of completely inhibiting the sensitizing power of the reagin, the reagin lacks the property of inactivation of the atopen. In a recent study of the immunologic properties of the bovine reagin of ragweed sensitivity, the writer[45] has found a similar condition to exist in this species. In contrast to this, it is well known that anaphylactic antibody is completely neutralized by its corresponding antigen. The destruction of the atopic reagin by heat for one-half hour at 56° C. and the only slight alteration in the anaphylactic antibody by the same treatment was described by Coca and Grove[15] and later confirmed by Jadassohn.[28]

Contact Dermatitis. Allergic contact dermatitis is the phenomenon of altered reactivity of the skin caused by first contact with a sensitizing substance and manifested after an interval upon further surface contact with the original substance. In this category are included those sensitivities

formerly classified as dermatitis venenata, which is an eruption due to contact with poison ivy, poison oak, poison sumac, and other plants, and contact sensitivity to chemical substances. The absence of effect after first contact indicates that the plant oils or chemicals are not primary irritants. The appearance of dermatitis after subsequent exposure, however, establishes the allergic character of the condition.

In order properly to distinguish this group from various eczemas due to the atopic influence, a few points of differentiation can be made. That the atopic condition is influenced by heredity was early shown by Bonne,[4] Galewsky,[22] Darier,[18] and Brocq.[6] In fact, Jordan[30] was able to trace the transmission of atopic eczema through four generations. In contrast in contact dermatitis, stands the work of Straus,[52] who was able to sensitize the skin only after two or three surface applications of an extract of poison ivy. This lack of hereditary influence is further borne out by the work of Brown, Milford, and Coca,[7] who found that the incidence of success in sensitizing non-atopic skins is the same as that achieved in sensitizing atopic ones.

The presence of demonstrable reagins in atopic eczema and their absence in contact dermatitis have been reported repeatedly when using the transfer technique of Prausnitz and Küstner (Coca and Grove[14] and Bloch[3]). However, the presence of some sort of antibody has been suggested to be instrumental in contact dermatitis by the work of Urbach,[54] who has reported that vesicatory fluid from eruptions due to contact allergy is capable of inducing a passive sensitivity in normal skin.

It has often been shown that there is a necessity for direct surface application of the allergen in contact dermatitis, since positive reactions are never obtained through the use of intracutaneous injections. This, of course, is in direct contrast to the sensitivity of the atopic skin to the scratch, intracutaneous, and percutaneous (Herrmann[27]) methods of testing.

Serum Allergy (*Serum Disease*). The term "serum sickness" was presented in 1905 by von Pirquet and Schick[40] to describe the symptom complex developing after a primary injection of a foreign serum. It was early noted that these undesirable reactions, including urticaria, fever, rash, adenopathy, and others, were not evident immediately following the primary injection but, rather, were displayed some 8 to 12 days thereafter. This delay or incubation period has served as one of the differentiating features of the disease. Prior to the report of von Pirquet and Schick,[40] no generally acceptable explanation for the mechanism of the condition had been presented. In their monograph, however, they proposed that the reaction was due to the effects of a toxic substance that resulted from the interaction of a newly formed antibody with residual amounts of the antigen, *i.e.*, foreign serum, still present in the circulation. In the experimental evidence brought forth by these workers, it was further shown that, following a second injection into rabbits, the incubation period was either lacking or greatly shortened. They therefore suggested that this reduced incubation period was due to the presence of a preformed antibody from the previous injection. In their efforts to explain the observations on the basis of an antigen-anti-

body theory, these workers did not credit the precipitin as the mediating antibody. Indeed, they explicitly postulated some other unidentified antibody in this connection, pointing out that precipitin was not consistently present. This fact was further emphasized by the report of Tuft and Ramsdell[53] in 1929, which showed the almost complete absence of precipitins and anaphylactic antibodies in individuals who had received large doses of normal horse serum, even though many of them developed serum sickness. This was confirmed by Coca, Deibert, and Menger[14] by examing at two-day intervals the serum of 26 subjects to whom had been administered sizeable amounts of normal horse serum. In no instance were precipitins found, in spite of the fact that some of the subjects developed serum disease.

Fleisher,[29] studying serum sickness as occurring in the rabbit, concluded that "it has not been possible to demonstrate in rabbits affected with serum sickness any constant temporal relationship between precipitins and precipitinogens in the blood on one hand and of the occurrence of serum sickness on the other hand." That the mediating mechanism of the condition is, however, an antibody of some type, even though not precipitin, has now been established by Karelitz and Stempien[31] by using the technique of Voss. They have shown that serum from patients recovering from serum sickness exhibits the power of inducing an immediate attack of the disease when administered to horse-serum-treated individuals.

Drug Allergy. Closely allied to the foregoing serum disease is the condition of specific sensitiveness to drugs. This condition is exhibited in the sensitive individual by an unusual yet characteristic response to a drug, which response is lacking in most individuals. That these two reactions are closely related is evident from the facts that a common incubation period must transpire before symptoms are displayed and the almost identical list of symptoms is present in both diseases. The one stumbling block at the present in ascribing the same mechanism to both phenomena is the lack of antigenic properties of most of the excitants of the drug allergies.

Hypersensitiveness of Infection. That altered response to bacterial infections may be manifested in several forms within the body has been pointed out by several writers. Scherago[48] has cited bacterial hypersensitivity of the atopic type exhibiting the immediate type of reaction following intradermal exposure to filtrates or products of bacteria, bacterial anaphylaxis, and the tuberculin type of sensitivity. The mechanism of the first two is, of course, the same as that responsible for those types of sensitivity to other antigens.

The tuberculin type of specific sensitivity, on the other hand, is different from these two by the following distinguishing features:

(*1*) When the products, *i.e.*, filtrates, sonic extracts, *etc.*, are injected into the skin, instead of an immediate erythematous wheal and hyperemic flare being developed, as in simple atopy, a delayed inflammatory reaction sets in after several hours and progresses to reach a maximum size and intensity in 24 to 48 hours and then slowly fades by 72 or 96 hours.

(2) The reaction of the tuberculin type sensitivity is more severe, being indurated with some erythema as against the soft edematous reaction of atopy.

(3) The Prausnitz-Küstner technique of passive transfer of sensitivity cannot be demonstrated with the serum of tuberculin-sensitive subjects.

(4) Body cells from the tuberculin-sensitive individual are killed *in vitro* by exposure to the bacterial protein, whereas cells from the atopic- or anaphylactic-sensitive individual are not killed by contact with the specific agent *in vitro*.

(5) When the antigen is injected either subcutaneously or intravascularly in the tuberculin-sensitive subject, a slow reaction of severe illness and occasional death may take place. Illness does not start until some hours after the exposure to the antigen and death does not occur before eighteen to twenty-four hours. This is in contrast to the immediate collapse and death observed in anaphylactically sensitive individuals.

(6) Whereas, ordinarily, contact with any foreign soluble protein will induce anaphylaxis in the guinea pig, to produce the tuberculin type of sensitivity it is necessary for the animal to have had previous contact with the intact organism or virus before sensitivity to an extract can be demonstrated.

(7) There is a wide distribution of body cells which are tuberculin-sensitive, while unstriped muscle is the only shock organ in anaphylaxis.

Familial Nonreaginic Allergy. The oft-encountered negative reactions to diagnostic tests in known food allergic individuals long remained unexplained. A lead to the understanding and the development of a suitable diagnostic criterion came unexpectedly through a chance observation.

While studying the characteristics of a case of angina in which attacks had been precipitated by therapeutic doses of dilaudid, Coca[11] observed such a rapid heartbeat that the pulse could not be counted. Soon afterward, he noted in this individual that the symptoms of angina, as well as the accelerated pulse, followed the ingestion of certain foods. This observation was made in 1935. Since that time, many similar cases of suspected food allergies with the absence of positive skin tests have been examined. It has been noted that this specific tachycardia is consistently present. Coca was further able to show that the atopic reagins were absent by virtue of negative skin tests, as well as failures to transfer passively any sensitivity by the P K technique. This consistent absence of reagins prompted Coca to designate the class of disturbances as nonreaginic food allergies. This condition has been shown to be free of the atopic influence, even though the atopic shock organ may at times be affected. Examples of such occurrences are the so-called intrinsic asthmas and the group of nonreaginic eczemas.

Allergic Diseases of Animals

With the classification as a background, it is appropriate now to consider the diseases of lower animals in relation to the phenomenon of hypersensi-

tivity, so let us discuss the few conditions of allergic manifestations of domestic animals that have been described.

Atopy. Early work indicated that lower animals were capable of becoming experimentally sensitized and of showing signs of asthma after exposure to an offending allergen.

In an extensive study, Ratner[44] was able to demonstrate sensitivity in guinea pigs induced entirely by inhalation of dust antigens. The animals were exposed to the materials for varying lengths of time and observed for clinical evidence of sensitivity. In many of the guinea pigs thus observed, a syndrome of respiratory difficulties was induced which very strongly resembled clinical asthma of man. It is interesting to note that in some of the guinea pigs which did not develop this pulmonary involvement, anaphylactic sensitivity was, however, produced. Conversely, not all animals displaying the asthmatic seizures were capable of being thrown into anaphylactic shock. This paper is of especial interest, for it laid the basis for an understanding of clinical sensitivity of animals as induced by inhalation.

The first indications of atopic sensitivity in our domestic animals as indicated by positive skin reactions were presented by the reports of Schnelle,[49] Burns,[9] and Pomeroy.[42] These workers individually attempted to correlate the results of positive skin tests to certain food extracts with the presence of clinical evidence of sensitivity. Schnelle, in 1933, described the results obtained from applying intracutaneous tests with salmon and corn meal in two dogs known to be subject to eczema. Both of the animals reacted to the test injections, as well as to potato and wheat flour in one and pork and rice in the other. These positive reactions were further shown to be significant by trial feedings with diets containing these allergens. Typical eczema was produced in the subjects in three and six days following the start of the feeding tests. Although Burns did not use standardized extracts of a specific protein content, he was able to show that there were definite signs of allergic sensitivity to the foods after ingestion. Among the offending agents which he found to cause positive skin reactions upon injection in his patients, rice and tomatoes were found, upon feeding trials, to cause symptoms of gastro-intestinal disturbance as well as dermatitis of varying severity.

Little appeared in the literature for several years thereafter on atopic conditions in animal disease until 1941, when the report of Wittich[57] was received with interest. It was in this report that he described the first recorded analysis of the allergic mechanism of asthma in the dog. Wittich was able to establish the seasonal appearance of the symptoms, positive skin reactions to the inhalant, and passive transfer of the sensitizing antibodies to the skin of a non-sensitive animal of another breed. The sensitive animal had been suffering from seasonal attacks of sneezing, tearing, conjunctival injection, nasal blocking with watery discharge at times, and small circumscribed raised swellings about the face and body. These swellings were the cause of much violent scratching, resulting in large excoriations of the skin. Because of the owner's habits, the animal was usually removed in the summer to an area near a lake shore where the

incidence of pollenosis was low. At these times, there was a remission of symptoms in the dog. However, when she was brought back to her city home, the return was accompanied by an exacerbation of symptoms. Skin tests with the pollens most frequently involved in the patient's area resulted in positive reactions to giant and short ragweed, pigweed, prairie sage, and Russian thistle. The short ragweed and prairie sage produced the largest wheals with pseudopod formation. Shortly following the appearance of the positive skin reactions, signs of general disturbances were noted, including those symptoms formerly mentioned. These were promptly relieved by the administration of epinephrine by injection and inhalation. The further establishment of the atopic character of the attack was achieved by successful passive transfer of the sensitivity to a non-sensitive dog and human subject. During the following years of the animal's life, she received desensitizing injections of mixed pollens, to which she had shown positive reactions. Following the inception of this method of treatment, and until the death of the dog, no further symptoms of the sensitivity were observed.

No further evidence of atopic sensitivity in domestic animals was presented until 1943, when Weil and Reddin[56] reported on the existence of dermal supersensitivity to ragweed in a herd of cattle under their observation.

These workers established the presence of a sensitizing reagin which was capable of inducing sensitivity in the skin of a non-sensitive cow upon intradermal injection. This antibody was shown to be similar to the human ragweed reagin in that it was destroyed by exposure to heat at 56°C. for 2 hours. This study further revealed that the bovine species was able to produce a neutralizing antibody upon immunization with the specific antigen. It is not destroyed by exposure to a temperature of 56°C. and also can be produced by successive injections of the antigen in the non-sensitive subject.

In a later paper, Reddin[45] showed further that the properties of the reagin were identical with that found in human ragweed sensitivity, at least as far as certain immunologic properties were concerned. This study showed that the reagin was specifically inactivated by the corresponding antigen, even though it was unable to neutralize the antigen. It was further shown that reagin cannot be produced by continued injection of a non-sensitive cow with the specific antigen.

While data was being gathered for the second report, the entire herd was examined for the existence of dermal sensitivity, and it was found that 40 per cent of the animals exhibited some degree of reaction. The three cows which gave the strongest skin reactions were tested for ophthalmic sensitivity by insufflation of dry ragweed pollen into the conjunctival sac. Only one of these showed lacrimation and mild injection of the conjunctival vessels. During the following ragweed-pollen season, however, no signs of clinical sensitivity were observed.

The question of the existence of clinical pollenosis in cattle still remains unanswered. However, the ophthalmic reaction here cited would seem

to make the answer more than theoretical. In this connection, one should recall the cases of reputed typical hay fever in pure-bred cattle, as cited by Bray[5] in England. His report is, however, lacking in serological analysis, the diagnosis having been made on seasonal occurrence of symptoms only.

In the interim between these two reports on the bovine reagin, another example of reaginic sensitivity in the lower animal was presented. In 1944, Brunner and co-workers[8] were able to demonstrate the natural presence of skin-sensitizing antibodies in dogs, as evidenced by positive skin reactions to an extract of an ascarid. They further showed that, in the animals which were harboring these nematodes in their intestinal canal, the serum contained the antibody, and that it was capable of passively sensitizing the skin both of non-sensitive canines and of human subjects.

Contact Dermatitis. Landsteiner and Chase[33, 34] have been able experimentally to demonstrate contact dermatitis due to simple chemical substances and poison ivy in the guinea pig. Simon and others[51] have also experimentally produced dermatitis caused by poison ivy in the guinea pig, as has Straus[52] in the monkey. To my knowledge, however, naturally occurring contact dermatitis in lower animals was not reported until 1946. In that year, Reddin and Stever[46] presented a case report of a horse with an extensive dermatitis of three years' duration. The animal affected was a fine hunter-type horse which had received the best possible care. The skin had been treated by several veterinarians in various parts of the country without satisfactory results. The lesions were small raised areas, well circumscribed and apparently limited to the epidermis. They occurred over the neck, shoulder, and costal regions.

The location of these lesions suggested that there was a possible association with some substance used either in the tanning of the leather of the saddlery or in its cleansing or conditioning. It had been the practice, in this particular stable, to wash the saddlery with a popular saddle soap, followed by the application of a well-known leather conditioner. Inunction tests with these products separately caused no reaction to normal areas of the skin, but, when mixed and rubbed into the skin, pronounced local swelling resulted some hours thereafter. When the individual ingredients of the two products were tested both singly and in combination, negative reactions resulted, except in the case of a combination of one oil and a dye. The pigment, "wool yellow dye," and sulfonated neatsfoot oil, when mixed and applied, proved to be the offending substances. Relief was afforded by application of a bland oil preparation to the affected areas. Subsequent attacks of the dermatitis were avoided following the thorough cleansing of the leather and the use of a saddle soap which did not contain the pigment.

Serum Sickness and Drug Allergies. The earliest report of serum sickness occurring in animals is that of Béclère, Chambon, and Ménard[1] published in 1896. These writers noted the appearance of varied types of eruptions, fever, and evidence of disturbance of locomotion in cattle about four days after the injection of large amounts of horse serum.

Gerlach[23] reported, in 1922, the occurrence of symptoms of serum sickness

in horses and cattle upon injection of a heterologous serum. He found that the reactions in horses were less severe than in cattle and that the size of injection had little influence upon the severity of the attacks. A further observation made by this worker was that the sensitivity could not be transferred to the guinea pig by way of the serum from an affected animal, thus showing that he was dealing with serum sickness rather than with anaphylaxis.

In an extensive series of reports, Fleisher and his co-workers[20, 26, 29] have described the manifestations of experimentally-induced serum sickness in the rabbit. They have described the disease in two forms, that is, the delayed and accelerated types. The delayed reaction followed a primary injection of the foreign serum in from 3 to 8 days, while the accelerated reaction set in within 8 to 72 hours after a second injection. The symptoms most frequently observed in their rabbits included erythema and edema of the ears. The erythema was of the morbilliform or scarlatinal type. It was shown in these studies that there was no constant relationship between the presence of precipitins in the serum of the affected rabbits and the development of serum sickness. It was further found that there was an elevation of body temperature in about 53 per cent of the rabbits which developed the disease, but in those injected with the foreign serum that did not develop serum sickness only 22 per cent showed any degree of hyperpyrexia. Changes in the white cell content of the blood of afflicted rabbits were not constant, although there was occasionally a mild leucopenia associated with the appearance of the disease.

The incidence of allergies to drugs in domestic animals has received little attention. However, the increased use of antibiotic and chemotherapeutic agents in veterinary medicine can be expected to shed some light on the problem. That some allergic manifestation may at times appear to be the result of drug administration has been suggested by the reports of Klein[32] and Stubbs[36] and their co-workers. In the study of the pharmacology of sulfanilamide, Klein observed an urticaria in one cow. Subsequently, Stubbs used the same animal in studies involving sulfathiazole, and again observed a reaction of similar nature following the use of this second sulfonamide.

Non-Reaginic Food Allergy of Animals. The diagnosis of non-reaginic allergy, based primarily upon the change in pulse rate within a short time after exposure to the allergen, presents a particularly difficult problem to the veterinarian in clinical practice. Lower animals are subject to emotional disturbances which readily affect the heart rate, thereby confusing the interpretation of the test. Even though the use of this classical diagnostic test will be highly restricted, some progress may be expected by careful observation when employing elimination diets.

Some case reports from the literature are of interest in this connection. A baby walrus was captured in the Bering Sea and was bottle fed on cows' milk. Small eroding areas, which sometimes bled, appeared on her head and flippers. She developed a mild conjunctivitis and there was increased salivation accompanied by drooling. The feces were abnormally soft and flecked with mucus.

Schroeder[50] systematically studied the case. Changes in the diet were made to determine whether the condition represented nutritional deficiency. Careful observation of the lesions established that they were more severe shortly after each feeding. This led him to consider the possibility of an allergic reaction being involved. Withdrawal of the cows' milk was followed by an almost immediate remission of the severe signs. The lesions healed and the skin became smooth and dry, although scars remained.

Very recently, Povar[43] has presented a report of a series of cases which exhibited various signs of food allergy in dogs. Some dogs were affected with a hemorrhagic colitis of varying intensity. The condition appeared and disappeared rapidly, except in a few cases, where death resulted within 24 hours after the onset of hemorrhage. Death was prevented in other severe cases by resort to transfusions. Pathologic examination of one of the fatal cases revealed extensive submucous hemorrhage with cellular filtration of the colon. The blood vessels of the entire thickness of the intestinal wall were congested and dilated, while some vessels contained "an organized mass of blood clot which was granular and necrotic in appearance and extensively infiltrated with polymorphonuclear leukocytes." In some of the cases which did not terminate fatally, avoidance of horse meat and, in others, commercially prepared food resulted in the disappearance of symptoms.

The nature of the symptoms cited by these two writers and their similarity with symptoms observed in some cases of non-reaginic food allergy of man has led Coca[13] to believe that allergies of this classification do occur in lower animals.

The recognition of allergic diseases in lower animals has not been frequent. Since one or two examples of each class of allergy have been reported, however, the fact is established that lower animals possess the capacity to develop allergies with the same characteristics as those observed in man. Careful observation and the use, so far as is possible, of diagnostic tests may be expected to add additional examples. The importance of the field is self-evident, as recently expressed by Weil[55]: "Altogether a whole nearly unexplored field of research is open here for the mutual benefit of human and veterinary medicine, promising a harvest valuable in itself and for the sake of creating tools for experimentation."

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SERUM SICKNESS

By Samuel Karelitz

The Willard Parker Hospital and the Mount Sinai Hospital, New York

The term "serum sickness" was coined by von Pirquet and Schick[1] to describe the reaction of man to the injection of a heterologous animal serum. For 8–12 days after the injection of animal serum (horse) nothing abnormal is noted. After that, the patient with manifest serum sickness develops a rash, most often urticarial; fever; lymph-gland enlargement; edema; arthralgia; and leucopenia with a relative lymphocytosis. Von Pirquet and Schick described these signs and symptoms in great detail and ascribed them to a toxic substance which they believed resulted from a reaction between the antigen (horse serum) and antibody. This occurred only after the antibody had reached an adequate concentration. They noted that a second injection of the horse serum in the same person called forth another attack of serum sickness, but after a shorter period of incubation, 5–7 days (accelerated reaction), and in some cases an immediate reaction occurred within a few minutes. Von Pirquet and Schick demonstrated anti-horse serum precipitin in the blood of persons who were at the height of serum sickness, as did Hamburger and Moro.[2] Unlike the latter authors, von Pirquet and Schick did not think that precipitin was the antibody responsible for serum sickness, because some patients who developed serum sickness had no demonstrable circulating precipitin, while anti-horse serum precipitin was demonstrable in other patients who had been treated with horse serum but had not developed serum sickness. Furthermore, they were unable to demonstrate precipitin at the time of the immediate reaction which, in their opinion, was the most striking example of an antigen-antibody reaction.

Although the view that serum sickness is due to an antigen-antibody reaction seemed well supported by the clinical and experimental evidence presented by von Pirquet and Schick, this theory was questioned until Voss[3] demonstrated that serum sickness could be induced in horse serum-treated patients by injecting them with human serum obtained from persons convalescent from serum sickness caused by therapeutic horse serum. Harten and Walzer,[4] in their discussion of serum allergy, reviewed the work of Voss and of Szirmai[5] and all the available data pertaining to the antibodies obtained in serum sickness and concluded that the data failed to reveal a constant association of any type of antibody with serum sickness. They believed that the presence of antibodies in serum sickness convalescent serum (S.S.C.S.) had been assumed by Voss, since no antibody studies were reported. They agreed with the doubt previously expressed by Coca[6] that any circulatory antibody is responsible for serum sickness.

Since 1939, further studies[7] of induced passive serum sickness have been made. The results of some of these have already been reported. Coca[8] and Doerr[9] have accepted the findings as establishing the antigen-antibody nature of serum sickness.

The discussion which follows will present a brief summary of the observations reported by Voss and of our experience with passive serum sickness, reviewing both published data and those of unpublished studies carried out before 1942. An attempt will be made to establish the identity of delayed serum sickness and passively induced serum sickness and to show that passive serum sickness is caused by an antigen-antibody reaction, thus proving that delayed serum sickness is caused by an antigen-antibody reaction.

Finally, there will be a discussion of the antibodies detected in several specimens of S.S.C.S. and in sera obtained from horse serum-treated patients who had not yet developed serum sickness and the significance of these observations with regard to the nature of the serum sickness antibody.*

Observations of Voss. Voss, encouraged by the successful use of measles convalescent serum in prevention of measles, attempted to prevent serum sickness in 36 children treated with diphtheria antitoxin 1–9 days before by injecting into them 2–10 ml. of serum obtained from patients convalescent from serum sickness resulting from diphtherial antitoxin (horse serum), S.S.C.S. He observed that the injection of convalescent serum 1–3 days following the intramuscular injection of diphtherial antitoxin resulted in the development of urticaria localized at the site of horse serum injection within 5–30 minutes. When the convalescent serum was given later in the incubationary period of serum sickness, constitutional reactions resembling anaphylaxis resulted. Delayed serum sickness occurred in only one of the 36 patients.

Voss gave the following explanation for this phenomenon. He assumed that the convalescent serum contained antibodies to horse serum, which, if supplied to a horse serum-treated individual, might raise the antihorse-antibody titre high enough to produce a serum reaction according to the theory postulated by Von Pirquet and Schick. The reaction would result in elimination of enough antigen to prevent the occurrence of the usual serum sickness. Furthermore, Voss believed that such a reaction was an example of human anaphylaxis, similar to the reversed anaphylaxis reaction of animals demonstrated by Opie and Furth,[10] Kellet,[11] and Zinsser and Enders.[12] Voss suggested that this procedure be employed to demonstrate humoral antibodies in man by a more localized reaction, which he developed. He produced such a localized reaction by the following technique: 0.1 ml. of 1/10 to 1/1000 saline dilution of horse serum is injected intradermally into a non-sensitive individual. After 8–24 hours 1–5 ml. of convalescent serum is injected intravenously. A large urticarial wheal, 1–5 cms. in diameter, develops in 5–30 minutes at the site of horse serum injection if specific humoral antibody for horse serum is present in the convalescent serum. This local reaction was reproduced by Szirmai and by Hopkins and Wright,[13] who found that it is suitable for the purpose of demonstrating antihorse-antibody in human sera.

* Throughout this presentation, serum sickness will imply that it followed horse serum therapy. S.S.C.S., or convalescent serum, will signify human serum obtained during convalescence from serum sickness due to therapeutic horse serum. Passive serum sickness will indicate the serum sickness induced in horse serum-treated patients by the injection of S.S.C.S.

TABLE 1

EFFECT OF SERUM SICKNESS CONVALESCENT SERUM ON PATIENTS WHO WERE TREATED WITH IMMUNE HORSE SERUM

Number of cases	*Type of serum therapy*	*Serum sickness convalescent serum*		*Passive serum sickness*			*Subsequent serum sickness*
		Amount	*Number*	*General*	*Local*	*None*	
		ml.					
9	S.F.A. (B. of H.)	2–10	1	3	5	2	9
6	S.F.A. (B. of H.)	10–15	2	0	0	6	6
8	S.F.A. (B. of H.)	3–10	3	3	5	2	6
5	S.F.A. (B. of H.)	4–10	4	5	1	1	2
1	S.F.A. (B. of H.)	5	5	1	1	0	1
2	S.F.A. (B. of H.)	4.5	6	1	1	0	2
1	S.F.A. (B. of H.)	4	7	1		0	1
7	S.F.A. (B. of H.)	2–5	8	4	5	0	4
1	S.F.A. (B. of H.)	5	9	1	0	0	0
6	S.F.A. (B. of H.)	3–10	10	0	0	6	3
46	Total			19	18	17	34 or 73.9%
4	L.S.A.	2–10	1	0	2	2	0
1	L.S.A.	5	2	0	0	1	0
2	L.S.A.	5–10	3	0	0	2	0
1	L.S.A.	3	8	1	0	0	0
8	Total			1	2	5	0
2	C.S.F.S.	5–10	1	0	1	1	0
3	T.A.T.	2–5	4	1	3	0	0
2	Dip. A.T.	4–10	4	1	2	0	0
1	Influenza S.	2	5	0	0	1	1
		Control Cases					
4	S.F.A. (B. of H.)	0.1-1 ml. H.S. in 10 ml. saline		0	0		2
3	S.F.A. (B. of H.)	10–20 A.S.		0	0		3
2	S.F.A. (B. of H.)	7 ml. C.S.F.S. 1 ml. S.F.A.		0	0		2
3	S.F.A. (B. of H.)	7–10 ml. C.S.F.S.		0	0		2
4	L.S.A.	10 ml. S.S.		0	0		0
2	Untreated scarlet fever	5 ml. S.S.C.S. #3		0	0		0
		5 ml. S.S.C.S. #4		0	0		0

S.F.A. (B. of H.), Scarlet Fever Antitoxin (New York Board of Health).
C.S.F.S., Scarlet Fever Convalescent Serum.
L.S.A., Refined Commercial (Lederle).
H.S., Horse Serum.
A.S., Human Adult Serum.
T.A.T., Tetanal Antitoxin.
D.A.T., Diphtherial Antitoxin.
S.S.C.S., Serum sickness convalescent serum.

Review of Author's Data on Passively Induced Serum Sickness. TABLE 1[7] reveals the statistical analysis of the results when, using 10 different convalescent sera, we attempted to produce passive serum sickness in 46 persons previously treated with scarlet-fever antitoxin, a horse serum prep-

aration consisting predominately of pseudoglobulin. The local reaction appeared in 18, and the general reaction in 19 cases treated with convalescent serum. Seventeen failed to show any reaction at all.

Passively Induced Serum Sickness—General Reaction. Clinically, the general reaction was typical in appearance to serum sickness. The rash was most commonly urticarial. The eruption first appeared at all sites injected with horse serum or at sites previously irritated by heat, cold, or xylol and was followed quickly by generalized itching, erythema, and urticaria. In two instances, a scarlatiniform rash appeared and in three, the urticaria was accompanied by angioneurotic edema of the lips and eyelids. In two cases, arthralgia was experienced and several developed fever. When the reaction lasted 24–48 hours, the passive serum sickness seemed to have initiated and merged with the delayed serum sickness, creating, in fact, an induced accelerated serum sickness. Both the urticarial and the scarlatiniform eruptions responded to adrenalin.

Passively Induced Serum Sickness—Local Reaction. The local variety of passive serum sickness conformed with that described by Voss. The localized urticarial wheal appeared 5 to 30 minutes after the injection of convalescent serum, except in an occasional case, when it appeared only after several hours. It occurred on all sites prepared with horse serum intradermally and lasted for about an hour.

Specificity of Reaction—Horse Serum vs. Antihorse Antibody. Specificity of the reaction for horse serum-treated individuals was shown as follows: (TABLE 1) S.S.C.S. induced the passive serum reaction when it was injected intravenously into patients treated 1–9 days before with tetanal antitoxin, diphtherial antitoxin, or scarlet-fever antitoxin, all horse serum preparations. However, this passive serum sickness was not induced in patients treated with human serum preparations, such as the scarlet-fever convalescent serum, and rarely in patients treated with refined scarlet-fever antitoxin prepared by pepsin digestion. Thus, it was shown that the antibody to horse and not an antibacterial antibody or antitoxin was significant in the production of passive serum sickness. Furthermore, it was not possible to induce passive serum sickness in patients treated with therapeutic horse serum (scarlet-fever antitoxin) 1–9 days before by the injection of normal human serum or normal horse serum. Serum sickness did not develop when cases of untreated scarlet fever received injections of serum sickness convalescent serum known to induce this reaction in patients previously treated with horse serum. Thus, it was also shown that passive serum sickness could be induced only in horse serum-treated patients when the S.S.C.S. which was used came from a patient who had had horse serum therapy.

Incubation Period in Passive Serum Sickness. Similarity between passive and delayed serum sickness was further advanced by showing that just as an incubation period is necessary for the production of delayed serum sickness, so was an incubation period found necessary for the production of passive serum sickness. This period was found to be in excess of one hour and less than 8 hours after treatment with horse serum.

Thirty-four children[7b] were treated with scarlet-fever antitoxin and with 5 c.c. of one of 4 specimens of serum-sickness convalescent serum simultaneously or within 5 minutes. Some of these children were injected intramuscularly with a combination of S.S.C.S. and the therapeutic horse serum mixed in a test tube immediately before the injection. Others were injected with therapeutic horse serum, and, through the same needle left *in situ*, the S.S.C.S. was promptly introduced. Others were simultaneously injected with the therapeutic serum in one buttock and the S.S.C.S. in the other. Passive serum sickness did not develop in any of these cases. In one child, local induration developed at the injected site, more suggestive of an inflammatory process than of an allergic response.

Table 2

Passive Transfer of Antibody to Horse Serum in S.S.C.S. by Technique of Voss

S.S.C.S.	*Amt. injected*	*Positive reactions*	*Negative reactions*
	ml.		
1	2–5	5	0
2	2–5	0	3
3	2–8	9	0
4	2–8	12	0
5	3–5	10	0
6	3–10	1	2
7	3–10	1	2
8	2–5	5	0
9	2–5	6	0
10	2–15	0	8
11	2–3	2	0
12	2–3	1	1
13	2–3	2	0
14	2	4	0
15	2	2	0
16	2	2	0
Total cases (78).....		62	16

Passive Transfer Studies. In subsequent studies,[7c] in order to further the evidence for the antigen-antibody theory of serum sickness, the passive transfer of the antihorse-serum antibody contained in S.S.C.S. was attempted. The techniques of Voss and of Prausnitz-Kuestner[14] in the usual and in the reverse order were employed. The technique of Voss is that previously described for demonstrating humoral antibodies in S.S.C.S.

Table 2 reveals the results obtained using the Voss technique with the first 16 sera studied. Using this technique, positive reactions were obtained in 62 out of 78 trials. Thus, transferable antibody to horse serum was demonstrated in 14 out of 16 sera. It is noteworthy that the sera which regularly failed to elicit this reaction are the same ones which previously failed to produce serum sickness. We have repeatedly reproduced this passive reaction more recently with other specimens of S.S.C.S. and with 3 sera obtained from horse serum-treated patients who did not have clinical serum sickness.

Antigenicity of Normal Horse Serum and Fractionated Therapeutic Horse Serum for Passive Transfer Reaction. Normal horse serum was found as effective an antigen as therapeutic horse serum for skin preparations in demonstration of this passive transfer antibody in S.S.C.S. If, instead of normal horse serum, highly refined diphtherial antitoxin was used to prepare the skin for the passive transfer, the reaction occurred less regularly and was weaker when it developed.

Specificity of Passive Transfer Reaction. Specificity of the reaction between horse serum and the S.S.C.S. was shown as follows: The skin of 2 children was prepared with 0.1 c.c. of hog, sheep, and horse serum, and the skin of 4 others with cat, dog, guinea pig, human, monkey, rabbit, and horse serum. Twenty-four hours later, 2–3 c.c. of S.S.C.S. was injected intravenously into each child. Typical reactions, large urticarial wheals, appeared only at the sites prepared with horse serum, except for one slight and delayed reaction which appeared at the site prepared with sheep serum and one at that prepared with dog serum.

Passive Transfer by Technique of Prausnitz and Kuestner. The sensitizing antibody contained in S.S.C.S. was again demonstrated by the technique of local passive transfer as done in the Prausnitz-Kuestner reaction. Local passive transfer of this antihorse-serum antibody was also shown by this technique performed in the reverse order, namely by preparing normal skin with 0.1 c.c. of horse serum and subsequently testing with 0.1–0.2 c.c. of S.S.C.S. Positive transfers were attained with 6 out of 7 S.S.C.S. tested. Each serum was tested on 3–9 individuals.

A larger reaction resulted at the transfer site if the human serum which was used as the antigen, instead of horse serum, was obtained from patients who had received therapeutic horse serum 48–72 hours previously. It was also observed that the reaction was more pronounced if the transfer was performed in the reverse order of the usual Prausnitz-Kuestner technique. This same observation has also been made by Wright and Hopkins.

Effect of Heat on Passive Transfer Antibody. Heating two of the S.S.C.S. ℔ 8 and ℔ 9 in a water bath for 90 minutes at 56°C. failed to interfere with the ability of these sera to give positive transfer tests. Likewise, heating another serum, ℔ 14, to 60°C. for one hour failed to destroy its ability to react at skin sites prepared with horse serum. These experiments demonstrated a transferable antibody to horse serum which was thermostable to 56°C. for 90 minutes and to 60°C. for one hour.[15]

Skin Test for Horse Serum. Since the horse serum injected into a person is quickly distributed to all parts of the body and can be demonstrated in the skin within 24 hours by the passive transfer techniques of Voss or by the Prausnitz-Kuestner reaction, the skin should contain sufficient antigen to react to an intradermal injection of S.S.C.S. containing antibody. It occurred to us, therefore, that it might be possible to demonstrate horse serum antibody contained in S.S.C.S. merely by injecting 0.1 or 0.2 ml. of this serum into the skin of individuals recently treated with horse serum. The results of the skin-test study are summarized in TABLE 3.

The skin reaction of untreated individuals to S.S.C.S. is similar to the re-

action to normal adult serum, *i.e.*, a raised blanched area about 0.5 cm. in diameter which rapidly disappears. The reaction to an intradermal injection of 0.2 c.c. S.S.C.S. by a patient previously treated with horse serum is a larger wheal, which becomes urticarial in a few minutes, forming pseudopodia, and is surrounded by erythema. The wheal grows to 1–5 cm. during the ensuing 5–30 minutes, then recedes to become completely absorbed in about one hour. This reaction can be elicited approximately one day following a horse serum injection and thereafter until the patient develops serum sickness, at which time the skin reaction is variable in intensity. If a patient is tested while having serum sickness, an urticarial wheal may form and blend with the urticaria of the serum sickness, the skin may swell and become erythematous, or there is little more than the usual reaction to normal horse serum. After the serum sickness has passed (also in patients who

TABLE 3

SKIN REACTIONS TO S.S.C.S. #4 COMPARED TO HORSE SERUM IN PATIENTS TREATED WITH THERAPEUTIC HORSE SERUM

Days after horse serum therapy	*Number of cases*	*S.S.C.S.*		*Horse serum*	
		pos.	*neg.*	*pos.*	*neg.*
1	6	6	0	0	6
2	3	3	0	0	3
3–5	8	8	0	0	8
6–7	11	10	1	1	10
8	6	6	0	3	3
9	7	7	0	3	4
10	8	8	0	6	2
11	5	4	1	4	1
12	1	1	0	1	0
13	1	1	0	1	0
14	11	11	0	10	1
15	6	5	1	6	0
16–30	12	8	4	11	1

failed to develop serum sickness) the reaction to S.S.C.S. continues to be positive for a variable length of time after the injection of horse serum.

When the skin of a patient treated with horse serum is tested 24 hours later and daily thereafter with S.S.C.S. and simultaneously with horse serum, the reaction to the horse serum remains negative for about a week to ten days. During this same period of time the reaction to S.S.C.S. is positive (see FIGURE 1). The intensity of the reaction to S.S.C.S. increases for the first few days after horse serum therapy but becomes weaker when the horse serum begins to elicit positive reaction. After recovery from serum sickness and in horse serum-sensitive individuals, the reaction is usually more intensive to horse serum than to the S.S.C.S.

A skin area showing a positive skin reaction to horse serum ordinarily becomes positive again following an injection of horse serum into the same site on the next day. A site reacting to the S.S.C.S. shows little or no response to a second injection of S.S.C.S. injected into the same skin site the following day, while a skin site not previously tested gives a positive reaction.

The reactions to S.S.C.S. in an individual who has been previously treated with refined horse serum may be slight or negative. It was also noted that different batches of S.S.C.S. varied in their ability to elicit this reaction.

Summary

Thus far, we have demonstrated that passive serum sickness is clinically similar to delayed serum sickness and that both are due to antigen-antibody

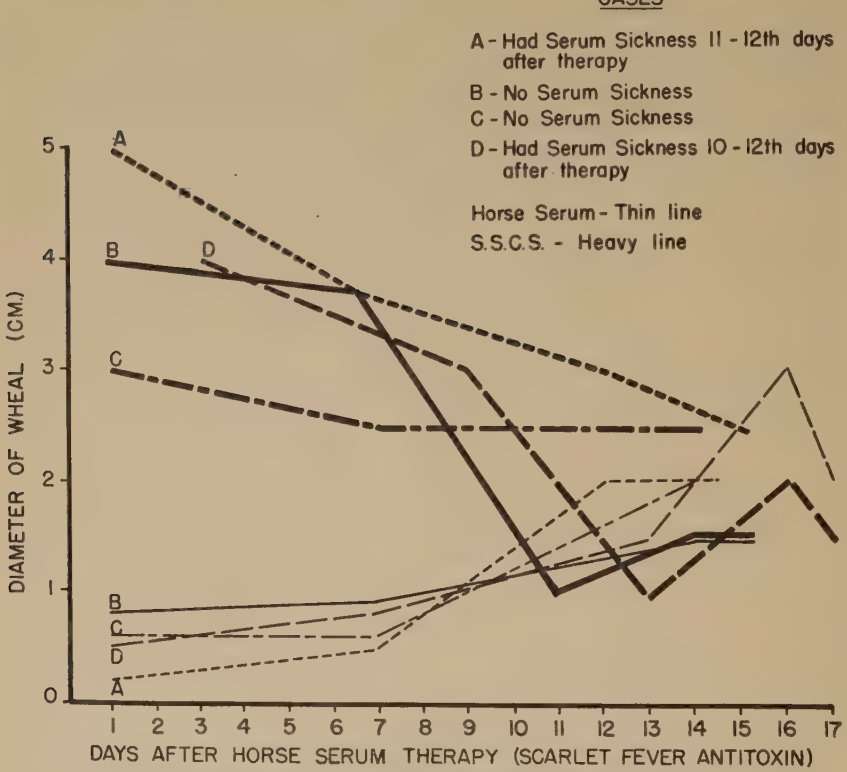

FIGURE 1. Skin test. Skin reaction of horse serum-treated individuals to intradermal injection of 0.2 ml. S.S.C.S. and comparison with skin reaction to horse serum.

reactions. An eruption, usually urticarial, fever, and joint pain are common to both, as is an incubation period. Passive serum sickness was shown to be a specific reaction of a horse serum-treated individual to convalescent serum obtained from patients who were treated with horse serum. Just as the incidence of delayed serum sickness is reduced by purification of the antiserum, so was the ability to reproduce passive serum sickness reduced by using purified therapeutic horse sera. It was possible to demonstrate this serum sickness antibody by the passive transfer reaction of Voss, by the local passive transfer reaction performed by the Prausnitz-Kuestner technique, and finally by the skin test.

Analysis of Antibodies in S.S.C.S.

The antigen-antibody nature of serum sickness having been demonstrated, an attempt was made to identify the antibodies contained in the S.S.C.S. and to determine the role played by them in serum sickness. Similar but less extensive analyses were made of several sera obtained from patients 14 days after they had received therapeutic horse serum, but who had not manifested clinical evidence of serum sickness. The results of these antibody determinations are presented in TABLES 4 and 5.

TABLE 4
ANTIBODY ANALYSIS OF S.S.C.S.

No. of S.S.C.S.	*Anti-horse precipitative titer*	*Heterophile agglutinative titer*			*Produces passive serum sickness*				*Skin test in horse serum-treated cases*	*Passive transfer (P.K.)*	*Inverse passive transfer (P.K.)*	*Direct passive anaphylaxis in guinea pigs*
					general		*local*					
		Non abs.	*G.P. abs.*	*Beef RBC*	*pos.*	*neg.*	*pos.*	*neg.*				
1	0	1/7	0	1/7	7	2	5	0	—	—	—	—
2	0	1/14	0	1/14	0	6	0	3	—	—	—	—
3	1/100	—	—	—	6	2	9	0	++	++	++	—
4	1/100	1/448	0	1/28	9	1	12	0	++++	++	++	Reaction & recovery
5	1/2000	1/14	0	0	1	1	10	0	—	—	—	—
6	1/50	1/28	0	1/14	2	0	1	2	++	+	+	Reaction & recovery
7	1/10+ 1/50±	1/14	0	1/14	1	0	1	2	+	+	+	Reaction & recovery
8	1/1000	1/448	0	1/112	5	1	3	0	+++	++	++	Reaction & death
9	1/100	1/448	—	—	8	0	10	0	++	+	+	Reaction & death
10	1/1000	1/512	—	—	0	6	0	8	0	0	0	Reaction & death

Symbols: —, not done; +, positive; 0, negative; P.K., Prausnitz-Kuestner.

Findings of Table 4. Of the 10 different S.S.C.S. tested for precipitin by the ring test and with the collodion particle technique of Freund,[16] 2 gave negative reactions. Five out of 9 gave positive heterophile agglutinative reactions in titers of 1/28 or stronger, and 5 out of 7 of these sera tested for heterophile agglutinative antibody were slightly positive after absorption with beef erythrocytes. Passive serum sickness was produced with 8 of the 10 sera. Passive transfer of antihorse-serum antibody was accomplished with 6 of the 7 sera tested and the skin test was positive with the same 6 sera. Passive anaphylaxis in guinea pigs was demonstrated with all of the 6 sera tested.*

All of the 6 sera which were shown to contain anaphylactin also contained

* Techniques used: for each serum tested, 4 guinea pigs, each weighing about 250 grams, received subcutaneous injections of the S.S.C.S., and, after 18–24 hours, each received 2 cc. of horse serum intravenously.

precipitin, and only 5 of the 6 produced passive serum sickness. High precipitin titers did not always occur with high heterophile agglutinative titers nor with the ability of the particular serum to produce passive serum sickness. The sera with especially significant findings will be discussed individually.

Serum ⁂1 gave a negative test for precipitin but produced passive serum sickness in 7 of 9 attempts and the local reaction of Voss in 5 out of 5.

Serum ⁂5 caused irritation of the skin into which it was injected, making it difficult to interpret the passive transfer results.

Antibody Reaction to Normal Horse Serum. Serum ⁂8 was obtained from a scarlet-fever patient who had recovered from serum sickness following an injection of 40 ml. of normal horse serum instead of therapeutic serum. Normal serum was given so that her antibody response could be followed on the basis of the observations made by Coca[17] and Tuft and Ramsdell[18] that the antibody response of healthy persons to normal horse serum was very weak even though these patients developed serum sickness. It is noteworthy that the serum sickness which this patient developed was accompanied by the development of antibodies in high concentration. The precipitin titer of her serum was positive against horse serum in 1/1000 dilution. The heterophile antibody titer was 1/448 non-absorbed and 1/112 after absorption with beef erythrocytes. Her serum produced passive serum sickness regularly.

The antihorse antibody contained in this serum could be transferred to normal skin. The serum produced the positive skin test in horse serum-treated persons and it caused passive anaphylaxis in guinea pigs. Possibly the difference between these observations and those made by Coca[17] after he had treated healthy American Indians with normal horse serum is that our patient was reacting simultaneously to a bacterial infection and to horse serum. Thus, possibly, an enhanced reaction to the horse serum resulted. Perhaps this might be compared to the induction of high precipitin and colloidal agglutination levels in guinea pigs by Freund and McDermott[19] by the injection of horse serum in a suspension of paraffin oil, falba, and killed tubercle bacilli.

Antibody Response to Pepsin-Digested Scarlet-Fever Antitoxin. Serum ⁂10 was obtained from a patient whose serum sickness resulted from treatment with 15 c.c. of pepsin-digested refined scarlet-fever antitoxin. His serum sickness was moderate. The convalescent serum had a high titer for precipitin and heterophile antibody. It produced passive anaphylaxis in guinea pigs, yet, despite this and the high precipitin titer, it failed to induce passive serum sickness and passive transfer reaction or to produce a positive skin test in horse serum-treated individuals. The implications of these observations will be discussed later.

Antibody Formation without Developing Serum Sickness. The sera obtained from 3 patients, 14 days after they had been treated with scarlet-fever antitoxin, yielded significant findings (TABLE 5). These patients did not develop clinical serum sickness. The serum of 2 of the 3 had no demonstrable precipitin; yet all produced the local passive serum reaction. All had heterophile antibody but their nature was not determined.

Antibody Response in Horse Serum-Sensitive Person. Serum #14 was obtained from a 12 year-old colored boy who was ill with scarlet fever. Five minutes after 0.5 c.c. of a 1/10 dilution of scarlet-fever antitoxin was injected intradermally for a blanching test, he began to complain that his skin was hot and itching. Generalized urticaria with angioneurotic edema developed, especially at the eyelids, tongue, and pharynx. He became dyspnoeic, then unconscious. Artificial respiration and oxygen inhalations were given. Ten milliliters of calcium gluconate were injected intravenously and epinephrin intramuscularly and intravenously. He emerged from the stupor and two hours after his episode he felt well subjectively. However, his eyelids remained swollen for 24 hours. No further evidence of serum sickness developed. It was learned later that he was an asthmatic, but sensitivity

TABLE 5

ANTIBODIES DEMONSTRATED IN SERUM OBTAINED FROM PATIENTS (11, 12, 13) WHO WERE INJECTED WITH THERAPEUTIC HORSE SERUM 12–14 DAYS BEFORE BUT WHO DID NOT DEVELOP CLINICAL SERUM SICKNESS; FROM PATIENT 14, WHO WAS ASTHMATIC AND HAD AN IMMEDIATE REACTION; FROM PATIENT 15, WHO HAD SERUM SICKNESS AFTER TREATMENT WITH PEPSIN-DIGESTED SCARLET-FEVER ANTITOXIN, AND PATIENT 16, WHO HAD SERUM SICKNESS WITHOUT A RASH

	Serum sickness	*Antihorse precipitin titer*	*Heterophile agglutinative titer non abs.**	*Produces passive serum reaction*				*Inverse passive transfer reaction P.K. technique*
				general		*local*		
				pos.	*neg.*	*pos.*	*neg.*	
11	0	0	1/128			2	0	—
12	0	0	1/32			1	1	—
13	0	1/100	1/32			2	0	—
14	+	0	1/10	1	0	4	0	+
15	+	0	1/80			2	0	+
16	+	1/100	1/160			2	0	+

* Guinea pig and beef R.B.C. absorption not done.
Symbols: —, not done; +, positive; 0, negative; P.K., Prausnitz-Kuestner.

to horse serum or horse dander was not known previously. Serum prepared from his blood, drawn 10 days after this episode, gave a negative reaction for precipitin and only a low titer (1/10 unabsorbed for the heterophile agglutinative antibody). Yet, this serum reproduced both the local and general forms of passive serum sickness and contained the passive transfer antibody for horse serum.

Effect of Benadryl on Antihorse-Antibody Formation. Patient #15 had serum sickness following treatment with refined diphtheria antitoxin, 20,000 units intravenously and 20,000 units intramuscularly. The serum sickness was treated with Benadryl (50 milligrams, 4 times daily) with what seemed to be a favorable effect on the itching and urticaria. Blood was drawn 72 hours after medication was discontinued and 6 days later, all clinical evidence of serum sickness had disappeared. No precipitin was demonstrated, but the serum did produce the local form of passive serum sickness.

Antibody Formation Following Serum Sickness without a Rash. Serum

#16 was obtained from a child who was treated with 5 ml. of scarlet-fever antitoxin. After 7 days, he ran an unexplained temperature which persisted for several days. Serum sickness was suspected, although no rash appeared. On the 14th day after treatment with antitoxin, his blood was drawn. It revealed the presence of precipitin, a heterophile antibody, and ability to produce the local passive serum reaction, the latter even after the serum was heated at 60°C. for one hour, thus establishing the thermostability of this serum sickness antibody. In accordance with the findings of Loveless, this antibody lacks the thermolabile quality of a reagin. Since this is a single observation, confirmation is necessary before thermostability of the serum sickness antibody can be concluded.

Discussion

The data of analysis of the antibody determinations permit certain deductions as to the nature of the serum sickness antibody. The presence of this antibody would seem to be established if a particular serum is able to produce passive serum sickness in a horse serum-treated patient. Passively-induced serum sickness, the local serum reaction demonstrated by the Voss technique, the passive transfer reaction demonstrated by the Prausnitz-Kuestner technique, and the skin reaction of horse serum-treated patients to intradermal injections of antihorse antibody-containing serum are all similar reactions except in degree. Therefore, it may be concluded that a positive reaction demonstrated by any one of these techniques indicates the presence of the serum sickness antibody.

Using these criteria for the demonstration of the serum sickness antibody, it was established that it occurs in most patients convalescing from serum sickness, that it may be found in horse serum-treated individuals who do not develop clinical manifestations of serum sickness, and that it may appear in patients who are treated with normal horse serum. It was also shown that the serum sickness antibody was present in the blood of a horse serum-sensitive patient 10 days after a severe immediate reaction to horse serum.

The serum sickness antibody seem to have no constant relationship to the heterophile antibody. This observation is in keeping with the demonstration by Powell *et al.*[20] that horse serum from which the heterophile antigen had been removed was still productive of serum sickness. Likewise, the serum sickness antibody and the anaphylactic antibody did not invariably occur simultaneously and seem to be distinct. One of the 6 sera which produced anaphylaxis in guinea pigs failed to induce passive serum sickness.

Finally, the data show that the presence of precipitin seems to have been unrelated to the presence of the antibody responsible for production of the passive serum sickness reactions. Of the 16 sera tested, only one had no precipitin and failed to induce passive serum sickness, while 5 of the 16 contained no demonstrable precipitin but did possess the ability to induce passive serum sickness reactions. Of the 13 samples of S.S.C.S., 4 had no demonstrable precipitin, yet 3 of the 4 sera did induce passive serum sickness reactions. Of the 3 sera obtained from horse serum-treated patients who had no clinical evidence of serum sickness, only 1 contained precipitin, but all 3 produced the localized form of serum sickness. The most important

observations against the views expressed by Hamburger and Moro,[2] Longcope and Rackeman,[21] Mackenzie and Leake,[22] and others—namely, that precipitin and the serum sickness antibody are identical—are those made with S.S.C.S. # 10. This serum had a high titer for antihorse precipitin. It produced anaphylaxis in guinea pigs but failed consistently to induce any of the reactions ascribed to the serum sickness antibody.

These data corroborate the original views expressed by von Pirquet and Schick, namely, that serum sickness is the result of an antigen-antibody reaction and that the serum sickness antibody is distinct from precipitin.

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CONTACT ALLERGY OF THE SKIN

By Max Grolnick
Jewish Hospital, Brooklyn, New York

After definition and identification of the subject, this presentation will be primarily concerned with the mechanism or manner of the development of contact allergy. An attempt will be made to present such pertinent experimental data from the available medical literature as may aid in the formulation of a logical hypothesis for such a mechanism. The introduction of a vast literature on the clinical aspects of contact dermatitis will be avoided, except in particular instances where the experimental data suggest some clinical implication. Thus, many excellent clinical presentations by the later students of contact allergy, such as Schwartz, Sulzberger, Downing, Stokes, Shelmire, Epstein, and others will be omitted. Highly controversial aspects of the subject will not be entered into.

Contact allergy is a manifestation in the skin of an inflammatory reaction, in response to an acquired hypersensitiveness to previous contact with an effective, specific, sensitizing substance. It can be reproduced at will by topical contact with the same or a related allergenic or sensitizing material. Clinically, it is represented by a superficial inflammation of the skin, generally with vesiculation, fairly sharply delineated, appearing in acute or chronic form and tending to recur. The specific diagnostic reaction, the patch test, is of the delayed and not the immediate whealing type, occurring in the already sensitized subject usually after twenty-four hours of suitable surface contact. It may appear after contact for a few hours or several days. There is no evidence of an inherited predisposition, a characteristic distinguishing it from the skin manifestations commonly referred to as atopic eczema or dermatitis of infancy or neurodermatitis of early childhood and early adult life.

Contact dermatitis is commonly encountered in civilian medical practice and may be caused by a variety of substances such as poison ivy and other similar plants, by household materials, cosmetics, clothing dyes, adhesive plaster, and others. Injudicious and continued use of some local therapeutic agents may cause prolongation of the original lesion by inducing new sensitivities. Contact allergy is of special import among the various dermatoses encountered in industry, particularly since the advent of the newer synthetic products. Bonnevie,[1] in a discussion of the occupational dermatoses, stated that eczema (contact dermatitis) was a disease of civilization, having become more prevalent with industrial expansion.

Contact allergy involving the skin is variously referred to as eczema ("Ekzem" of the European school), eczematous contact-type dermatitis (Sulzberger), dermatitis venenata, or epidermitis (S. Epstein). In this presentation, the general clinical entity just identified will be referred to for the most part as contact dermatitis, though the term eczema may be used at times in referring to the older literature.

Josef Jadassohn[2] was the first to report on untoward (allergic) reactions

in the skin due to certain drugs administered internally or parenterally. He made observations on the clinical phenomena which were involved in the causation of eczema and referred to such factors as sensitization, incubation period, and method of spreading of the sensitization. He also presented his concept regarding the ability of the skin to react by means of the surface application to the skin of the suspected agent. This was referred to as the "functioneller Hautprüfung" or functional test of the skin, now commonly called the patch test. Several modifications of the original technique are in general usage. Bloch[3] employed the term "eczema test" and specified five degrees of reaction ranging from erythema to tissue necrosis.

Histopathology

According to Bloch and Steiner-Wourlisch,[4] the pathologic process in human eczema affected most strongly the cells of the epidermis and the underlying layer of the dermis. In the milder reactions, the participation of the connective tissue was slight. The authors felt that the involvement of the epidermis was characteristic of eczema and served to differentiate it histologically from simple inflammatory reactions. Sulzberger[5] stated that the predominating shock organ in contact dermatitis was the epidermis and that the cutis participated to a lesser degree, if at all. The initial lesion was intraepidermal edema, known histologically as spongiosis. Following this, the lesion was evident as intraepidermal vesicles, which when fully developed were visible clinically as blebs of varying size, some of which oozed readily. In a comparative histologic study of the various eczematoid dermatoses, however, Sachs, Miller, and Gray[6] detected little intercellular edema or spongiosis about the epidermic vesicles and little evidence of edema in the rest of the epidermis. In the upper cutis and sub-epidermic zone, there were dilatation of the vessels and some interstitial edema. In addition, there was found here a moderately diffuse cellular infiltration of small round cells and wandering connective tissue cells. Rokstad[7] felt that histologic investigation could hardly determine whether the epithelial changes were primary or secondary to the alterations in the blood vessels in the corium. The writer has observed a number of times that the first visible evidence in the development of the spontaneous flare-up reaction was a petechial-like eruption at the site of application of the sensitizing agent, and that this was present even before there was palpable edema at the site. It would appear then, from a consideration of these reports, that, in addition to the part played by the epidermis, the structures in the papillary and upper cutis zones are involved in the pathology of contact allergy of the skin.

The histology of the specific lesion of contact dermatitis would appear to differ in no wise from that of the non-specific one. Miescher[8] reported the histologic response in the sensitive individual to be the same as that induced by the application to the skin of primary irritants such as croton oil, turpentine, cantharides, and others. Mom and Noussitou[9] demonstrated similar findings at both the actively sensitized specific site (dinitrochloro-benzene) and at that produced by an irritating concentrated solution of the same

excitant. The skin showed initial intraepidermal spongiosis and vesicle formation, and in the later stages there was lymphatic perivascular infiltration of the vessels of the papillary body and superficial dermis.

In a comparison of the specific reaction in man with that in the guinea pig, produced by painting the skin with ragweed oil or 2-4 dinitrochlorobenzene, Ginsberg, Becker, and Becker[10] and Ginsberg, Stewart, and Becker[11] demonstrated considerable histologic difference. In the animal, there was a slight intracellular and intercellular edema, but definite spongiosis was not seen. Vesicle formation was lacking. The cutis showed diffuse edema and round-cell infiltration. In man, however, the edema tended to be localized in the epidermis, where it led to vesicle formation, and in the cutis round cell infiltration was predominantly perivascular. The authors felt that these differences were to be explained not by a disparity in the degree of reaction but, rather, by the dissimilarity in structure of animal and human skin.

In evaluating some of the experimental material to be presented hereinafter, it is essential to bear in mind the apparent similarity between the specific and non-specific cutaneous reaction, and the lack of similarity between the animal and human cutaneous response.

Mechanism of Development of Contact Dermatitis

In considering the role played by allergy and immunology in the mechanism of contact allergy of the skin, it is well to look back to a presentation by Coca[12] in 1926 on the relation of human hypersensitiveness to anaphylaxis. He stated that the task of confining his paper to studies having some bearing on the conditions of hypersensitiveness affecting human beings was "difficult because nearly every question to be presented is in active controversy." In fact, very little space was devoted to any discussion of the subject of contact dermatitis. Certainly, in the past two decades, there has been a most significant advance in the understanding of the various agencies which affect the development of skin sensitization of this type.

The subject of mechanism, which will constitute the major part of this paper, will be presented under four general divisions, namely: (1) factors involved in active sensitization; (2) manner of spread of sensitization; (3) immunology; and (4) chemical hypersensitiveness.

(1) Factors in Sensitization. The requisites for inducing sensitization of the skin are a suitable sensitizing agent, an experimental subject which is capable of responding in an allergic manner to exposure to this substance, and a method of contact between subject and allergenic substance which will stimulate the immunologic processes.

The Sensitizing Substance. Bloch[4] stressed the importance of a specifically active substance. Thus, though poison ivy, primula extract, and formalin were able to sensitize large numbers of subjects, camomile accomplished this infrequently. The concentration of the excitant was likewise of significance. When the human skin was treated by a dilute preparation of the primulin plant, only 42 per cent of the subjects were sensitized. The use of a concentrated extract was effective in sensitizing all the subjects. The

strength of the excitant also influenced the time of appearance of the sensitization. Thus, when Silverberg[13] treated the same area of skin in humans with a daily unction of a 10 per cent ointment of mesotan (salicylic ester), the incubation period was 20 to 25 days. When a 100 per cent ointment was employed, sensitivity occurred in 7 to 10 days.

It was stated by Stauffer[14] and others that a substance, to be a good sensitizing agent, must be a primary irritant when used in high concentration. Simon, Simon, Rackemann, and Dienes[15] observed that the skin of guinea pigs always reacted to the first application of poison-ivy extract with redness and swelling of the skin. Wedroff and Dolgoff[16] noted the primary irritation caused by a strong solution of 2-4 dinitrochlorobenzene. Landsteiner and Jacobs[17] asserted that most substances which were capable of sensitizing were in themselves irritating, though such an effective excitant as paraphenylene-diamine had little primary action on the skin, and some irritating chemicals were incapable of inducing sensitization. Straus,[18] on the other hand, was unable to find any irritation on the skin of newborn infants, at sites treated with a strong poison-ivy paste, or on the skin of the Rhesus monkey[19] treated with an undiluted poison-ivy oil for several days.

Clinically, the frequent establishment of sensitivity, after apparent healing of a vesicated skin, induced by direct contact with irritant chemicals used in the manufacture of poison gases was observed by Goldblatt.[20] The likeness in gross appearance between the specific and non-specific lesions of contact dermatitis was observed by Bonnevie[1] and others, and the similarity in histologic picture was referred to previously.[8, 9]

Exposure to Allergen. The necessity of exposure to the excitant has been established as a requisite in the development of sensitivity. Spain[21] demonstrated the absence of any reactions to poison-ivy extract in 18 infants from 5 weeks to 18 months of age. Reactions, however, were obtained in a group of children past the age of 8 years and in adults. On an expedition to the Baffin Islands, Heinbecker[22] was unable to elicit any skin response to tests with concentrated poison-ivy extract in 65 normal Eskimos. Likewise, Straus[18] found that 119 newborn infants failed to react to the first patch test with poison-ivy extract. The application to the skin of a paste made of equal parts of lanolin and ivy residue for a 6- to 8-day period did not produce any skin response, but, when the infants were tested from 2 to 4 weeks later, there was an incidence of positive reactions of 73 per cent. Among the subjects tested by Grolnick[23] to determine the existence of sensitivity to krameria, there were 26 children, ranging from 8 months to 13 years of age. No positive reactions were obtained, but four of the children became sensitized by the 48-hour test, after an incubation period of from 8 to 15 days.

Technique of Sensitization. The methods used in active sensitization of experimental subjects employed, for the most part, some means of surface contact of the sensitizing substance with the skin. There were some variations in the general technique. Low[24] sensitized himself and one other to primula extract by treating the skin from which the horny layer had been removed. The same method applied to 6 others was ineffective. Bloch

and Steiner-Wourlisch[4] rubbed primula extract into the intact skin or into sites traumatized with "glass paper." When necessary, this procedure was repeated up to 10 times, utilizing various locations on the body. The application of a concentrated extract succeeded in sensitizing all of 12 human subjects after 1 to 3 treatments, in most instances after the first. Schwarzschild[25] sensitized his subjects by applying orthoform daily to the same area of skin and covering the site after each treatment with an adhesive plaster patch. Muller[26] employed the same technique in sensitizing humans with a 2 per cent ursol (paraphenylenediamine) ointment applied on either the intact or abraded skin. Newborn infants were sensitized by Straus[18, 27] by means of a single prolonged patch-test application of a strong poison-ivy extract.

Wedroff and Dolgoff[16] introduced the drop-method technique in their experiments in active sensitization of humans. They succeeded in rendering sensitive 70 per cent of their subjects with a drop of a 10 per cent solution of dinitrochlorobenzene. This method has since been used extensively for experimental sensitization of animals or humans.

Straus[19] applied the undiluted poison-ivy oil as a patch test to the skin of the Rhesus monkey for 48 hours without initial response. A similar test made 7 to 10 days later yielded a typical contact reaction. Grolnick,[23] in sensitizing human subjects to krameria, a plant extractive, employed the technique of repeated patch-test applications of the excitant for 1 or 2 days at spaced weekly intervals. If sensitization failed to occur after 8 such treatments, a final patch test was applied for a 7-day period. Of 37 subjects studied by this method, 86 per cent were actively sensitized. In unpublished experiments, it was found that an initial 7-day treatment yielded an even higher percentage of successful results, most of them occurring after the initial application. These techniques enabled the writer to make a critical study of the flare-up reaction.

In summary, active sensitization of the skin of experimental subjects was readily induced by surface treatment of the intact or traumatized skin, with a concentrated preparation of a potent excitant, either for a prolonged period or for shorter repeated periods of time. The various authors reported that sensitivity was generalized, as demonstrated by positive tests on any part of the integument.

Methods of rendering the skin sensitive by means other than surface application were also attempted. Frei[28] and Sulzberger[29] were able to sensitize the guinea pig by the intracutaneous administration of neoarsphenamine. They determined the existence of tissue sensitivity by means of an *intracutaneous test*. Sulzberger could not demonstrate sensitivity by similar test in animals treated by the intracardiac, intrapulmonary, intraperitoneal, intravenous, or intramuscular routes of administration. Simon[30] failed to sensitize guinea pigs to poison ivy by the latter three channels, yet succeeded by the direct application of the excitant to the skin. Straus[27] fed 10 newborn infants an alcoholic solution of poison-ivy extract, but could not elicit a positive test with the extract several weeks later. Nor was he able to sensitize infants by the subcutaneous injection of a similar extract.

Haxthausen[31] reported sensitization of the skin of humans with dinitrochlorobenzene introduced intracutaneously or subcutaneously. No other investigator has confirmed sensitization in humans by this procedure. Sensitization by the intramuscular route was achieved only when horse or human serum was added to the chemical. It was shown by Ginsberg, Stewart, and Becker[11] that guinea pigs sensitized by surface application of ragweed oil or poison-ivy extract attained the same degree of sensitization as those sensitized by its intracutaneous injection. But the authors claimed that contact tests with graded dilutions of the antigen were much easier to interpret than were the intracutaneous tests. Landsteiner and Chase[32] were able to demonstrate skin sensitivity in guinea pigs given intraperitoneal injections of picryl chloride or of conjugates of the latter and homologous red cell stromata, after preliminary treatment of the animals with tubercle bacilli. A high degree of skin sensitiveness was determined by the surface application of a dilute solution of picryl chloride. More recently, Strauss and Spain[33] reported the occurrence of contact-type reactions with poison-ivy extract in guinea pigs treated previously by intraperitoneal injections of aqueous alum-precipitated poison-ivy extract.

The view is held by some that contact-type dermatitis can occur clinically from influences other than external. Block[3] claimed that the eczematous reaction could arise experimentally by the ingestion or injection of iodine, quinine, resorcin, and arsphenamine in sensitive individuals. Horsfall[34] induced a characteristic exacerbation of dermatitis of the hands in a patient sensitive by contact to 1:8 million solution formaldehyde within $15\frac{1}{2}$ hours of inhaling the vapor in a dilution of 1:95,000. Adequate precaution to exclude direct contact of the vapor with the skin had apparently been taken. Fisher[35] reported the lighting-up of previously healed areas of sulfonamide (contact) dermatitis following the oral ingestion of the specific drug. And, finally, the eruptions which occur not uncommonly in ivy-sensitive individuals during oral desensitization treatment are well known. It is not always clear from the descriptions of the skin manifestations induced by these various procedures whether they are identical with typical contact dermatitis. Furthermore, it should be recognized that *these skin responses generally occurred in the already sensitive individual.*

The Experimental Subject. Many animals have been employed in the study of experimental contact allergy, but the guinea pig has been the most widely used. A critical viewpoint, however, is needed in correlating the findings in animals with those in humans. Von Adelung[36] sensitized the rabbit to rhus toxin and the leaves, though most later observers did not find the rabbit to be suitable for study. Stewart and Cormia[37] were able to sensitize guinea pigs by repeated applications of nickel salts to the same skin area but failed to do so by intracutaneous injections with the same substances. These authors stated that Walthard succeeded in sensitizing by surface treatment of the skin with nickel but that Coca and Milford failed to confirm these findings.

Dienes[38] referred to the production of skin sensitization in the guinea pig with a number of chemical substances known to cause industrial eczema:

diphenylamin, phenylhydrazine, nickel, salvarsan, and the plant excitants, primula and poison ivy. Rabbits treated under the same conditions failed to respond. Brunsting and Bailey[39] sensitized 3 of 14 guinea pigs to the oily extract of the ragweed plant, but Kile[40] was unsuccessful with the plant oils of giant ragweed, sage, or orris root.

Straus[19] did not feel that the guinea pig, rabbit, or white rat were satisfactory for the study of sensitization to poison ivy, inasmuch as there was, at times, a marked initial irritative response. The Rhesus monkey did not present such a disadvantage. The fully developed mild reaction in this animal exhibited a sharply demarcated erythematous elevated area with superimposed follicular papules which oozed or bled easily. Scaling, which followed, lasted for a few days. The marked reaction consisted of erythema, elevation, central vesicobullae, and surrounding follicular papules. The picture was similar to that which occurred in humans. This description was in sharp contrast to the deep inflammatory reactions occurring in the guinea pig.

Grolnick[41] failed to sensitize the skin of the chicken with krameria by the method of successive applications of the excitant at spaced intervals. When poison ivy was employed as the excitant, sensitization was induced in 5 of 8 birds and was questionable in 1. The appearance of the reaction in successive stages was as follows: an initial erythema followed by small punctate hemorrhages; then an elevation of the follicles of the skin, rendering them palpable. Next, there was a faint edema represented by a palpable thickening of the skin, and this was followed by visible edema and vesicle formation. The vesicles were extremely fragile, so that the skin was readily denuded, with consequent oozing and crusting. The crusts were pale yellow at first (from admixture with the serous fluid) and later became dark. The reactions were fairly well limited to the sites of application of the excitant. These responses had been observed by H. Straus, who commented on their close resemblance to those elicited in the sensitized monkey.

Landsteiner and DiSomma[42] claimed sensitization of 60 per cent of 38 guinea pigs by repeated surface applications with diazomethane, a non-aromatic substance known to cause hay fever and asthma in lab workers. Description of the lesions suggested an irritative type of reaction. These authors also reported sensitization of two or three hogs to mustard oil by the same method and failures in guinea pigs, rabbits, and monkeys. The skin of the duck was found by Mirsky and Goldman[43] to be satisfactory for the production of bullae with various skin irritants such as croton oil, formaldehyde, and mustard oil. Microscopically the fluid was found to be subepidermal, the epidermis remaining intact.

Thus, from an extensive review of the role of the experimental animal, it would appear that the response in the monkey most closely resembled the human lesion, and that, while some findings obtained from guinea pig studies are applicable to man, others cannot be so correlated. It might also seem worthwhile to explore the possibility of further study with the fowl.

The human subject lends itself to investigations of the problem of contact allergy. Horsfall[34] did not believe that the erythematous papules ob-

tained by intracutaneous testing of a markedly formaldehyde-sensitive patient were entirely specific. These reactions resembled those described by Landsteiner and his co-workers in sensitized guinea pigs. Wedroff and Dolgoff[16] preferred humans in their studies, for they believed that the findings in experimental animals were not applicable to man. Sulzberger and Baer[44] and Sulzberger and Rostenberg[45] stated that the contact type of reaction in the human skin was not identical with the skin sensitivity demonstrated in the guinea pig by means of the intracutaneous test or even by surface application of the excitant. Furthermore, the human subject presented an advantage, in that the experimental approach paralleled the manner of clinical exposure, and the reaction was the same clinically and histologically as the disease. Haxthausen[46, 47] employed various surgical procedures in his studies on the manner of spread of sensitivity in the human subject. Later, considerations in the mechanism of evolution of contact allergy will point out the advantages of the use of the human as an experimental subject.

The Flare-Up Reaction. This phenomenon is the first visible evidence that a subject previously non-sensitive has developed a state of hypersensitiveness. The term was used by Frei[48] to describe the spontaneous appearance (*Aufflamungsphänomen*), in the human, of deep inflammatory reactions at the sites of intracutaneous tests with neosalvarsan introduced 11 to 12 days previously. The flare-up reaction was likewise observed after a 5 to 6 day interval in guinea pigs treated with the same drug.[28] Sulzberger[29] confirmed the findings in the guinea pig. The authors explained this change as the reaction between the then hypersensitive cells and the sensitizing substance remaining at the site of the injection. Dienes and Simon[49] described flare-up reactions in guinea pigs at the sites of intracutaneous tests with human serum given 5–6 days prior. By using several antigenic substances, a variation in their ability to produce flare-up reactions was found, turtle egg being effective in nearly all animals, human serum in only one of four. Egg white and horse serum were capable of producing hypersensitiveness but not spontaneous flares. Reactions of a similar nature to bacteria were demonstrated by Andrewes, Derick, and Swift[50] and by others.

The spontaneous flare-up as a manifestation of acquired hypersensitiveness of the skin (contact allergy) has been reported by most investigators either by name or description. The term should be used only where the activation of a previously inactive site is implied. The phenomenon occurs at the culmination of the incubation period and indicates the advent of a state of hypersensitiveness. It probably signifies an interaction between hypersensitive skin cells and an allergenic substance. The term should not be employed to indicate the lighting-up of the healed site of a specific test or a clinical dermatitis which may follow the appearance of a positive specific patch or surface test.

Bloch and Steiner-Wourlisch[4] discussed the lighting-up of old, totally or partially healed sensitizing sites (*Impherde*). They were probably dealing with what is now considered to be the spontaneous flare-up, inasmuch as the skin areas treated with primula extract had frequently been traumatized,

and, for this reason, the authors referred to healed sites. Schwarzschild[25] likewise referred to the activation of sensitizing sites in his experiments with orthoform. Wedroff and Dolgoff[16] described the flare-up reaction at the site of application of a drop of dinitrochlorobenzene after an interval of 8 to 24 days. At first, there was an initial erythema which was soon followed by a typical allergic contact-type reaction. Sulzberger and Rostenberg[45] observed flare-up of the sensitizing sites in over 50 per cent of their subjects. This occurred from 7 to 20 days after application of a drop of p-nitrosodimethylanilin and 2-4 dinitrochlorobenzene.

Grolnick[23, 51] undertook a systematic study of the flare-up reaction in humans sensitized with krameria. Eighteen subjects exhibited a typical flare-up response from 8 to 21 days following a single patch-test application with the excitants. Nineteen subjects were sensitized with from 2 to 5 successive applications of the allergen at weekly intervals. In these subjects, the appearance of a response, the flare-up reaction, at the final site of treatment was followed in 15 subjects by a spontaneous flare-up of the site of the preceding application, which up to that time had remained unchanged. In four additional subjects, flare-up occurred at two preceding and previously negative sites of application. These sites, moreover, were affected in the reverse order of their treatment and reacted in the majority of instances with less intensity than the initial flare-up reaction. The interval which elapsed between the time of treatment of these late responding areas and the appearance of the spontaneous reactions at these sites was from 10 to 43 days. Thus, the allergenic or antigenic substance had remained and apparently could stay fixed in the skin cells for as long as 43 days.

Another phase of this study was the determination of the minimal threshold of sensitivity to krameria, *i.e.*, how much of the excitant was available in the skin at the time of the spontaneous response and was therefore needed to evoke a reaction. Involved in this question, too, was the relation of the reverse order of flare-up to the concentration of the excitant at the respective skin sites. Thus, in further studies, patch-test applications were made horizontally on one arm, one or more inches apart, with an undiluted solution of the excitant, with 1:10, and with 1:100 dilutions. The patches were removed after 24 hours. The subject was then actively sensitized by making one or more applications of the undiluted excitant to the opposite extremity. The order of flare-up of the sites to which the graded dilutions of the excitant had been applied was then observed. Finally, as soon as flare-up occurred at the site to which the weakest dilution of the excitant had been applied, the subject was patch-tested with the excitant in dilutions of 1:1000, 1:10,000, and 1:100,000 in order to determine the level of sensitivity at this particular stage. The following findings were observed: The site to which undiluted excitant had been applied responded first in all six subjects. The site treated with 1:100 dilution always flared last. In 3 of the subjects, the level of sensitivity was demonstrated by a weak reaction at the site of the 1:100,000 dilution, in 2 by stronger reactions at the site of 1:10,000 dilution, and in 1 by a reaction with the 1:1000 solution. Applying these results to the findings of reverse order of flare-up reactions in

diminished intensity, it is apparent that the sites treated first had lost most of the excitant and that their reactivity had diminished during the inactive stage so that it was equivalent to that elicited by a solution many thousand times weaker than the original excitant.

The Incubation Period. As it relates to the experimental subject, the incubation period represents the time interval which elapses between the initial contact with an allergenic substance in a non-sensitive subject and the first appearance of a specific response at the site of exposure. Obviously then, the flare-up reaction signifies the culmination of those immunologic processes which have been stimulated by the primary exposure during this period. Where a single simple contact on a small area was effective in sensitizing the subject, there has been found a striking uniformity in the limits of the incubation period, namely from 7 to 24 days, regardless of the allergenic substance employed or its manner of application. Bloch and Steiner-Wourlisch[4] found the incubation period for sensitization of the guinea pig with primula extract by simple inunction to be 7 to 10 days. By the drop method in humans, Wedroff and Dolgoff[16] demonstrated a range of 8 to 24 days for dinitrochlorobenzene. With the same procedure, Sulzberger and Rostenberg[45] induced sensitiveness to dinitrochlorobenzene or to p-nitrosodimethylanilin in from 7 to 20 days. Straus[19] reported the onset of sensitivity in the monkey 7 to 10 days following the simple patch-test application with poison-ivy extract. Grolnick[23] found the incubation period for sensitizing humans with krameria by means of a single patch-test exposure to be 8 to 21 days.

When sensitization procedures other than a single contact were employed, the range in incubation period became less uniform. By making daily applications with orthoform, Schwarzschild[25] sensitized humans in from 10 to 71 days. Silverberg[13] found an incubation period of from 20 to 25 days for sensitization to mesotan by daily inunction with a 10 per cent ointment. When a 100 per cent paste was used, the interval was reduced to 7 to 10 days.

Occasionally, a shorter period than seven days has been reported. Thus, Milford,[52] in testing a group of ragweed-sensitive hay fever patients by the intracutaneous method with a suspension of ragweed-pollen oil in 1 per cent alcoholic solution, noted the development in some cases of a severe dermatitis at the sites of the tests in from 5 to 21 days. It would appear that these were instances of sensitization by surface contact with the allergenic oil.

Most observers reported the change in response of the skin which occurs once sensitization has been effected. Reactions then appeared to suitable contact tests generally in from 24 to 48 hours, and not infrequently within the first 24 hours. Thus, the reaction time must be distinguished from the incubation period (Sulzberger[5]).

Sensitization by Patch Test. While this topic primarily carries clinical implications, it is entered into at this point because of erroneous conclusions presented by a number of otherwise careful investigators on the incidence of sensitivity to poison ivy. By patch-test studies with poison-ivy extracts

in various groups of subjects, an incidence of positive reactions of from 49 to 76 per cent was reported: Spain, 65 per cent;[21] Deibert, Menger, and Wigglesworth, 59 per cent;[53] Spain, Newell, and Meeker, 75 per cent;[54] Knowles, Decker, Pratt, and Clark, 49 per cent;[55] and Keeney, Sunday, Gay, and Lynch, 70 per cent.[56] A detailed consideration of each report would be too lengthy at this point, though analysis of several of these studies was made in a previous publication.[51] All of these investigations are subject to the same criticism, namely, that a highly concentrated extract of poison ivy, or the actual leaf itself, had been used and the period of application of the patch tests was for 2 to 7 days. It seems certain that many of the subjects had been actively sensitized, as can be ascertained not merely from a study of the available tables but from such statements by the authors as "reactions were noted after as long an interval following application of the patch test as 27 days," or, "reactions were observed from 20 to 228 hours after the test." One should then interpret the values of 49 to 76 per cent not only to include the incidence of sensitivity to poison ivy but, in addition, to denote to what extent sensitization could be induced with this excitant by the technique employed, *i.e.*, the susceptibility of humans to this allergen.

Further analysis of the report by Spain, Newell, and Meeker revealed that successive applications of the excitant had been made in increasing concentration, thus adding an additional factor which aided active sensitization. In a consideration of the manner of development of sensitization by a single or by repeated patch-test applications with the excitant, it was stated by the writer[51] that each successive stimulus to the skin with the excitant influenced the immunological processes which were developing, and that the final outcome or state of hypersensitiveness was the result of a summation of the individual stimuli. Certain clinical inferences may be drawn from the above findings, namely, that, when patch tests are done as a diagnostic procedure, some active excitants in sufficiently high concentration may sensitize even with a single short exposure. Also, the not uncommon practice of repeating diagnostic patch tests with the same or related allergens when tests are negative or doubtful should be discouraged. It is not improbable that the repetition of some diagnostic patch tests by one or several clinicians may actively sensitize the patient to some of the substances being applied in the tests.

Another observation which pertains to the possible influence of the patch test is the statement by Wedroff and Dolgoff[16] that, when sensitivity which had been actively induced was in the stage of regression, repetition of tests could restimulate the sensitization process. Likewise, one should examine critically a statement made by Stauffer,[14] a careful clinical investigator, that, because a patch-test reaction did not appear in 1–2 days, it was not to be assumed that the test was negative. The author had observed cases in which it did not appear for 15 days and was then particularly intense. Downing[57] and Bechet[58] recognized the potential sensitizing feature of the patch test and for this reason the former opposed the pre-employment test.

Susceptibility. This term will be used to signify the extent to which

active sensitization can be induced under favorable circumstances in subjects not previously exposed to the specific excitant. It represents the organism's propensity for being sensitized. The susceptibility of humans to sensitization with various excitants has been referred to previously, namely, primula extract (100 per cent),[4] dinitrochlorobenzene (70 per cent),[16] poison ivy (73 per cent),[18] orthoform (45 per cent),[25] and krameria (87 per cent).[23]

The influence of a personal or family incidence of allergy (atopic mechanism) was studied by several observers. No such relationship was found. Brown, Milford, and Coca[59] showed that sensitivity to ragweed oil occurred with equal frequency in both atopic and non-atopic subjects. A similar observation was made by Grolnick[23] in his studies with krameria. Schwartz[60] found that a personal or family history of allergic diseases was not preponderantly present in those affected with industrial dermatitis. Knowles, Decker, Pratt, and Clark[55] determined by testing a group of 200 medical students with poison-ivy extract that there were no significant differences in the incidence of a personal or family history of allergy among those who reacted as compared with those who did not.

The possible transmission of skin sensitivity of the contact type from parent to offspring has been the subject of study by several observers. Kile and Pepple[61] showed that offspring of guinea pigs sensitized with poison-ivy extract before or during pregnancy were not themselves sensitive. Grolnick[62] failed to detect any sensitivity in the newborn infants of 7 mothers sensitized to krameria in the last 2 trimesters of pregnancy. In 4 of the parents, the reaction of sensitization was in an active phase when the infants were born, indicating a high degree of sensitivity in the mother at this stage. Chase[63] tested the offspring of guinea pigs who were highly sensitive to dinitrochlorobenzene or poison ivy with the specific excitant, but in no instance could transfer of sensitivity be observed. In contrast to this absence of transfer of contact type allergy, the regular transmission of anaphylactic hypersensitiveness produced by tuberculo-protein from mother guinea pigs to their offspring was demonstrated by Corper and Stoner.[64]

The presence of individual variations in susceptibility in humans has been emphasized by a number of investigators. Since the experimental animals varied even more in susceptibility according to species and within the species, the use of the human subject has been preferred by some for such studies. Wedroff and Dolgoff[16] were able to sensitize 50 of 72 subjects with eczema of various types with a 10 per cent solution of dinitrochlorobenzene, but in 20 normal persons it was more difficult to accomplish this, and frequently a 30 per cent solution had to be used. Sulzberger and Rostenberg[45] simultaneously sensitized both control subjects and groups of patients with healed or recent contact dermatitis with p-nitrosodimethylanilin and 2-4 dinitrochlorobenzene. Not only were there individual variations in accepting sensitization with each chemical, but, in addition, the subjects with recent or active contact dermatitis were more readily sensitized (91 per cent to one or the other) than the non-contact group (53 per cent). This

suggested that patients with recent or existing allergic dermatitis were more readily sensitized by exposures to other chemicals than were previously unexposed persons.

The individual variation in susceptibility is evident likewise by a study of the following findings by Grolnick.[23, 51] Of thirty-seven subjects sensitized by from 1 to 5 repeated applications of krameria at weekly intervals, 18 required one patch-test application, 8 needed two, 6 had three, 4 had four, and 1 required five such contacts. In the guinea pig, Ginsberg, Stewart, and Becker[11] demonstrated that animals sensitized to dinitrochlorobenzene showed no greater tendency to become sensitized subsequently to ragweed-plant oil than did previously unsensitized animals or horse serum-sensitized (skin) ones. Chase[63] was able to show a general tendency for guinea pigs to be sensitized to the same extent to two common excitants of contact dermatitis—poison ivy and dinitrochlorobenzene. In individual animals, the comparative degree of sensitization varied, however, for each chemical.

The differences in species in their responses to attempts at sensitization were discussed in part under the heading, "Experimental Subject." In addition, Landsteiner and DiSomma[42] were able to sensitize the hog with allylisothyocyanate (mustard oil) but failed to do so in the guinea pig, monkey, and rabbit. Grolnick sensitized humans readily with krameria, but was unable to do so in the monkey, an animal easily sensitized by Straus[19] with poison-ivy extract.

The influence of heredity on susceptibility to sensitization of the contact type was studied by Landsteiner and Chase[65] and Chase.[63] Guinea pigs were reared under controlled conditions. Colonies of animals which reacted to chemical sensitization to a high or low degree were established. The parents were mated within each group. With continued selection of parents who were high reactors, there was an increase in the number of offspring who were readily sensitized. Among the progeny of low reactors, the incidence of resistance to sensitization was increased, but the results were less uniform and there were none of high reactivity. The authors concluded that chemical sensitization of the contact type was influenced by heredity.

In summarizing the subject of susceptibility, it is evident that there are marked species differences, in addition to those differences found in individuals in the species. There is no agreement as to whether individuals previously sensitive are more susceptible to sensitization by another excitant. An atopic influence in contact dermatitis was not found by several observers. Finally, the work of Landsteiner and Chase showed that, by selective inbreeding, a strain which is highly susceptible to skin sensitization can be developed.

Permeability of Sensitized Skin. Some clinicians have maintained that cutaneous areas which had been the seat of contact dermatitis showed positive patch-test reactions with the specific excitant, whereas adjacent and previously uninvolved areas did not respond. It was assumed that these reactions were specific in character and indicated a heightened or localized

tissue hypersensitiveness at the affected areas. Thus, Bloch[3] stated that, in eczema, sensitivity varied regionally in intensity and that tests could be positive only in certain areas, particularly where the greatest contact with the offending substance had taken place. A state of local sensitivity was implied, a condition originally referred to as such by Jadassohn[66] in a case of odol "eczema." Stauffer[14] concurred in this viewpoint, yet in a contradiction in the same paper stated that it was possible to get stronger reactions on normal skin than at the site of a previously healed eczema, ascribing this to local desensitization. Other observers have followed more or less the same line of reasoning, *e.g.*, Strandberg,[67] Boström,[68] and Sulzberger.[5]

It has been the impression of the writer that such variations in reactivity of the skin can be ascribed to a change in permeability at the involved areas so that these sites are readily influenced by *non-specific* factors. Grolnick, Bowman, and Walzer[69] studied the state of responsiveness of the skin at a healed site of contact dermatitis. They observed that when an area of skin in an atopic individual had become specifically sensitized as a site of contact dermatitis and was allowed to heal, subsequent testing of these sites with the specific wheal-inducing atopens, such as ragweed or dander extracts, revealed an altered response to the latter tests. Wheal formation at the dermatitis sites was greater in most instances than at normal comparative sites in the same individual. The more intense the original dermatitis, the more pronounced was the tendency to increased wheal formation. Grolnick[70] then studied the response of healed sites of contact dermatitis to the subsequent application of a second and unrelated allergenic excitant. Reactions were elicited in 42 subjects who were sensitive to either krameria or poison ivy, but not to both. The sites were allowed to heal completely. After a 4- to 12-week interval, each site was retested with the other excitant. In most instances, control tests had also been made on uninvolved skin. In 14 of the subjects, a typical contact-type reaction was present at the sites which had been twice stimulated. In 10 of the subjects on whom controls had been done, these sites were negative. In 4 subjects, there had been no controls. One must infer from this experiment that, although the second response, to all appearances, seemed like a specific reaction, it could not be so interpreted, inasmuch as control tests had been negative. The role of non-specific stimulation of a specifically sensitive area will be taken up by the writer in another communication. It is felt that the findings just described are related to the subject of so-called local sensitivity.

(2) Manner of Spread of Sensitization. An explanation of the means by which sensitization of the skin becomes generalized following application to a small area of a suitable sensitizing agent has been sought by a number of investigators. One method of study was through isolation of the treated area by surgical or chemical means. Simon[30] applied poison-ivy extract to local areas of skin in 12 guinea pigs. These sites were excised at intervals varying from 1 hour to 4 days. Spread of sensitization was prevented if the excision was done less than 18 hours after such treatment. Landsteiner and Chase[71] confirmed these findings in a similar experiment, determining that sensitization became generalized if the treated area was removed later

than 8 to 12 hours following the sensitizing application. In another study in the guinea pig, Simon[30] destroyed a ring of skin around the middle of the animal by cauterization with concentrated nitric acid, thus separating the front and hind parts of the animal. The posterior half was treated with poison-ivy extracts and both parts tested 10 days later. Reactions occurred in both halves. The author assumed that the spread of sensitization was not confined to the epidermis, but occurred by way of the blood stream or lymphatic system.

Straus and Coca[72] severed the continuity of the skin in the Rhesus monkey by a circular incision in the upper third of the arm. Application of a strong poison-ivy extract to the forearm resulted in sensitization of the part distal to the incision, but generalized skin sensitivity could not be demonstrated. When the experiment was carried out in reverse, there was failure to sensitize the forearm. The authors concluded that spread of sensitization was attributable "probably to a diffusion of the oily excitant through the oily substances normally present in the skin." In essence, these findings were confirmed by Schreiber and Mueller[73] and Schreus.[74] Islands of skin, the size of a half dollar, were isolated on the backs of guinea pigs by the removal of a narrow strip of skin, the incisions penetrating down to the muscle and fascia. The islands were painted daily with a 5 per cent solution of dinitrochlorobenzene until an "eczematous" reaction appeared on the 7th day. Testing the remainder of the body with a dilute solution of the excitant failed to elicit any reaction. In another group of animals, the experiment was performed in reverse, reactions appearing on any part of the integument excepting the isolated skin islands.

Landsteiner and Chase[71] attempted to show that mere severance of the skin did not prevent the spread of sensitization to the entire skin surface unless the continuity of the superficial lymphatic vessels overlying the skin muscle (panniculus carnosus) was interrupted. When skin islands were isolated in the guinea pig and then treated by application with a strong poison-ivy extract, spread of sensitization was prevented almost uniformly, provided the incision included the skin muscle. The authors advanced a theory of sensitization, namely, that the chemical agent reacted quickly with tissue substance to form conjugates and these were transported by way of lymphatic vessels into the blood stream. They failed to explain why sensitization of the skin did not occur after the deposition of the excitant either subcutaneously or intramuscularly—findings which they and other investigators had ascertained.

Haxthausen[46] likewise claimed the demonstration of a hematogenous spread. Areas of skin in the epigastria of 3 human subjects were treated with dinitrochlorobenzene. The borders of the treated sites were then incised through the cutis, but not down to the fascia. The incisions were made at several intervals, at the time of treatment of the skin, 3 days, and 8 days later. Eventually, sensitivity of equal intensity was demonstrated both within and outside the incised areas. The author felt that the incisions might have been too superficial to prevent spread of sensitization. The same author[47] sensitized an area of skin in one of each of two pairs of twins. After intervals of 28 and 38 days, respectively, skin flaps were transplanted

from the sensitized to the non-sensitive twin in each pair, and conversely. Three weeks later, when healing was complete, tests with the specific excitant, dinitrochlorobenzene, were positive only in the two sensitive subjects, both over the general skin surface and on the previously non-sensitive skin flaps. Whereas the author interpreted these findings as evidence of some factor conveyed through the blood of the sensitized subject, one could just as readily draw the conclusion that the normal skin flap had been sensitized by diffusion from the adjacent hypersensitive skin. Thus, in the interpretation of the results of the aforementioned studies involving the continuity of the skin, there is definite variance in opinion.

Another method of study of the spread of sensitization entailed an alteration of the area of skin which was to be sensitized. Simon, Simon, Rackemann, and Dienes[15] produced injury of a skin site in the guinea pig by treatment with cowpox virus. With the appearance of the infection, the site was treated with poison-ivy extract in an attempt to sensitize the animal. Subsequent testing with poison-ivy extract in these animals and in sensitized control animals revealed a more striking sensitivity in the latter group. Haxthausen[46] was able to suppress sensitization of the human skin to dinitrochlorobenzene by treating an area with carbon dioxide snow as late as 8 days following application of the sensitizing chemical. In another experiment in the guinea pig, if selected skin sites were first treated with the freezing agent and then treated with dinitrochlorobenzene immediately thereafter, or after 2, 4, and 8 days, sensitization was suppressed in 4 of 5 animals in each group (total of 25 animals). Rokstad[7] was able to inhibit contact-type reactions by compression of the local areas. Thus, alteration of the skin by some means made it possible to influence sensitization. Confirmation of these experiments is lacking, however. Mom and Noussitou[9] could not prevent sensitization in humans with dinitrochlorobenzene by prior novocaine block of the nerve supply.

All of the experiments just cited were concerned with the initial phase of the development of sensitization, before the appearance of such evidences of sensitization as the spontaneous flare-up or the presence of a positive 24-hour patch-test reaction. The writer[51] inquired into this latter phase of the problem through further study of the flare-up phenomenon. By way of summary, human subjects had been sensitized by means of 1 to 5 successive patch-test applications of krameria extract at weekly intervals. Sensitivity was evident when a typical vesicular reaction appeared at the last treated site (flare-up). This was followed in numerous instances by the spontaneous appearance of responses at one or more preceding and previously negative sites of application. Moreover, flare-up of sites always occurred in the reverse order to that in which they had been treated. It was then shown that the order of flare-up was determined by the amount of fixed allergen which remained at the involved site, *i.e.*, the most recently treated site possessed the largest amount of excitant and was therefore the first to flare up after sensitivity had been effectuated. The oldest site, on the other hand, was the last to respond, since most of the excitant had been eliminated.

It was to be expected, then, that with the onset of sensitization sites ex-

posed simultaneously to the same allergen would flare up at the same time. Thus, in a further study, the excitant was applied simultaneously to two different parts of the body, *e.g.*, both arms, or both thighs, or one arm and one thigh. Following this, successive sensitizing applications with the excitant were made either close to or at a little distance from one of the two simultaneously treated areas. It was found that in the majority of instances the flare-up occurred earlier and the reaction was at first more intense at the area which was closest to the final sensitizing site than at the one more distant. One would have to infer from these findings that there had been a slow diffusion, by way of the skin, of some sensitizing factor, either allergen or a reacting substance. For, if spread of this factor had been entirely by the blood stream, one should expect sites treated simultaneously with the same concentration of excitant to flare up at the same time.

A point in confirmation of these findings is the observation by Haxthausen[46] that, when sensitization appeared at the "spontaneous" site, reactions were demonstrated first in the proximity of this area but, in 1 to 2 days, all areas reacted. Finally, from all of the foregoing experiments, regardless of technique employed or the outcome, the very significant role of some part of the skin in the ultimate establishment of a generalized skin sensitivity is apparent. The skin is not merely the end point, it is also the medium.

(3) Immunology. Though the subject of immunology in contact allergy of the skin is closely integrated with chemical hypersensitiveness, it will be discussed first, and separately from it, for the purpose of orderly presentation. Some overlapping will occur of necessity.

In human contact dermatitis, the diagnostic test is the patch, surface, contact, or percutaneous test. Its functions and characteristics can be enumerated as follows: (1) it represents an actual reproduction of the clinical lesion in a local area involving the tissue which is the seat of the disease; (2) substances which are readily available and easily applied are used in the tests instead of prepared, biological products; (3) the nature of the local response is the same generally, regardless of the substance employed to elicit the specific reaction; (4) the reaction is specific, though it may not be etiologic in significance; (5) reactions are generally multiple, and this may be due in part to sensitivities acquired by topical remedies used in the treatment of the clinical dermatitis; (6) repetition of patch tests may cause new sensitivities; (7) healed patch-test sites may light up on repetition of tests; (8) lighting-up of the clinical dermatitis may be brought about by specific reactions to patch tests.

Though contact dermatitis represents a delayed type of allergic response and is elicited by the contact or patch test, several references in the literature to the occurrence of the immediate wheal type of reaction will be recognized. Horsfall[34] obtained immediate wheal and erythema reactions by intracutaneous tests with formolized proteins (human, rabbit, or horse serum) in a patient with a formaldehyde dermatitis. Passive transfer of the test was not successful. Intracutaneous tests with formaldehyde yielded

erythematous papules of the delayed type similar to those described by Landsteiner in guinea pigs. Precipitin and complement fixation reactions were absent. Confirmation of these findings has not been reported. Landsteiner and Jacobs[75] obtained wheal responses to scratch tests with conjugates in guinea pigs sensitized with protein conjugates of acylchloride, but no reactions were elicited with the simple chemical itself. Jacobs, Golden, and Kelley[76] reported wheal reactions by scratch test in guinea pigs rendered sensitive to simple chemicals of the anhydride group, particularly to citraconic anhydride.

In interpreting the demonstration of wheal-type reactions, cognizance must be taken of the fact the typical contact dermatitis (except the Horsfall report) was not under consideration. The presence of wheal-type reactions to non-protein substances has been variously reported in drug sensitivity or in allergic mucous membrane manifestations: Kern,[77] phthalic anhydride; Mitrani,[78] thiamin chloride; Feinberg and Watrous,[79] chloramine T and halazone; and W. Sherman[80] and Whittemore and de Gara,[81] sulfadiazine. Such findings, though establishing the ability of simple non-protein chemicals to produce wheal-forming antibodies (and reagins), may not be used in explanation of an immunological mechanism in contact dermatitis.

Passive transfer of reactions to such known excitants of contact dermatitis as iodoform, paraphenylenediamine, mercury, primrose, and others have been reported in the past by Bruck, Klausner, Meyer, Bock, Mayer, Bieberstein, and others (quoted by Landsteiner and Jacobs[17]). Bloch,[3] however, was unable to demonstrate passive transfer with "eczematogenous" substances and cited Coca as having had the same experiences. In all recent reports in the literature, successful passive transfer of contact-type reactions has not been observed. Landsteiner and Chase[87] transferred an immediate wheal reaction to a non-sensitive guinea pig with serum from an animal sensitized systemically with citraconic anhydride. But, here again, the authors were not dealing with contact allergy.

Sulzberger and Katz[83] were unable to transfer any excitant from blister fluid obtained from blisters produced by specific (poison ivy) and nonspecific irritants (mustard gas and lewisite). Pratt and Corson[84] likewise reported negative results with the contents of blister fluid from poison ivy-sensitive patients.

The possibility of passively sensitizing animals to simple chemicals was studied by Landsteiner and Chase.[82] Guinea pigs, previously made tuberculin-sensitive to enhance subsequent sensitization with chemicals, were readily sensitized by means of conjugates prepared from guinea pig red cell stromata and picryl-chloride. By injecting the peritoneal exudate from such animals into the peritoneum of normal guinea pigs, there developed in the latter a state of passive sensitization of the skin manifested by a positive reaction to the application on the skin of a solution of picryl-chloride in oil. The implications of this experiment are discussed under the next heading, "Chemical Hypersensitiveness."

Anaphylactic shock could not be induced by Muller[26] by means of an intracardiac injection of ursol in guinea pigs sensitized 8 to 14 days pre-

viously. Landsteiner and Van der Scheer[85] produced anaphylaxis in animals sensitized to azoproteins by injecting the uncombined group, the azo dyes. This work was confirmed by Fierz, Jadassohn, and Stoll[86] by means of Schultz-Dale studies of the uterine strips obtained from guinea pigs sensitized to a diazotized atoxyl preparation.

Landsteiner and Jacobs[75] claimed a relationship between anaphylaxis and skin sensitiveness. Anaphylaxis was produced by injecting picryl-chloride conjugates into animals previously made skin-sensitive to the uncombined chemical. This work was extended by Landsteiner and Chase.[32] By means of intraperitoneal injections with conjugates of picryl-chloride or 2-4 dinitrochlorobenzene, guinea pigs were rendered anaphylactogenic and also achieved a high degree of skin sensitiveness as determined by the surface application of a dilute solution of the uncombined chemical.

While it was the intention of the writer to omit reference to the chemistry of immunological reactions, it was not found possible to do so. The evolution of chemical concepts in immunological phenomenon will be discussed under the next heading.

(4) Chemical Hypersensitiveness. Obermayer and Pick[87] ascertained that proteins derived from the same species would become heterologous when treated variously by such chemical processes as iodination, nitration, and diazotization. Wolff-Eisner[88] suggested a hypothesis to explain sensitization by protein-free chemical compounds of known composition. He assumed that protein molecules became coupled with the chemical within the body to produce a full antigen and submitted the work of the above authors in corroboration of this postulate. Obermayer and Pick[89] and Landsteiner[90, 91] have placed immunological chemical specificity on a definite basis and, thus, have bridged the hiatus between immunology and chemistry.

In order to present the relation of contact dermatitis to the broad concept of immunochemistry in a concise form, the nature of those chemicals which are known to be common excitants of contact allergy will be discussed first. Then the broader concepts of chemical specificity will be examined.

In the early studies of contact dermatitis, substances of unknown composition were utilized, particularly plant products such as primrose and poison-ivy extracts. But these were later supplanted by chemicals of definite constitution. Bloch,[3] with the help of Karrer, isolated a pure crystalline substance with the formula ($C_{14}H_{18}O_3$) from the primula plant. It possessed the property of producing violent reactions in primrose-sensitive patients. Brown, Milford, and Coca[59] established the oily fraction obtained from short and tall ragweed pollen as the cause of ragweed-pollen dermatitis. It was found, also, that certain related plants contained a common allergenic excitant. Straus[27] obtained reactions with poison sumac in the majority of infants who had been sensitized to poison ivy. The common excitant of these two plants and of the Japanese lacquer tree was found to be urushiol, a mixture of substituted catechols of the average formula $C_6H_3 \cdot (OH)_2C_{15}H_{27}$ (Mason, *et al.*[92]). It was assumed that these plant substances

were rendered readily accessible to the skin by their miscibility with the natural oils of the skin.

Other allergenic substances, both of defined and less defined composition, have been referred to under a previous heading, "The Sensitizing Substance." Landsteiner and his workers employed chemicals of known composition for the most part. It is important, in correlating the work of these investigators with the topic of contact allergy of the skin, to recognize that they were primarily interested in the specificity of serological reactions and were able to demonstrate that the specificity of antibodies extended beyond proteins to include simple chemical substances. It also was their aim to establish a hypothesis for the immunological phenomena rendered by non-antigenic substances.

In their attempts to sensitize the guinea pig, Landsteiner and Jacobs[17] used various approaches: single or repeated injections; intracutaneous, subcutaneous, or intravenous routes; and direct application to the skin of the chemical in solution or ointment. Tests for sensitivity were made by the intracutaneous method or by direct application of the substance, and the reactions were read in 24 hours. They were recorded in terms of various shades of erythema and grades of infiltration (elevation) of the skin. Vesiculation, present generally in human reactions, was not observed as part of the responses in their animals. The authors stated that sensitization was most readily achieved by direct application of the excitant, and was least successful by the subcutaneous and intravenous routes. By the intracutaneous method, a course of several injections over a period of several weeks was more effective than a single injection. Furthermore, the authors observed that the lesions in animals did not appear to be of the same intensity as those demonstrable in human beings.

In the progression of his studies on specificity of serum reactions along chemical lines, Landsteiner utilized a method of attaching simple chemicals to proteins in order to prepare conjugated antigens containing specifically reacting components of known constitution. At first, acyl groups were introduced into proteins by treatment with anhydrides or chlorides of acids. Subsequently, a more reliable procedure was found to be the joining of proteins with diazonium compounds, designated as azoproteins. The azo-antigen was found to be specific for the azo-component and, to a small extent, for the protein portion of the antigen.

Landsteiner and Jacobs[75] noted a parallelism between the sensitizing capacity and the chemical behavior of certain nitro- and chloro-substitution products of benzene, namely, their lability when treated with alkali. The nitro- and chloro-radicals were loosely bound, so that the parent chemical readily formed substitution compounds with aniline by interacting with the amino group. The authors then postulated that, where sensitization of an organism occurred to simple chemicals, an interaction took place between the latter (hapten or partial antigen) and some constituent in the body, thus giving it antigenic and sensitizing characteristics. The anaphylactogenic property of such conjugated products had been demonstrated by Landsteiner and Van der Scheer.[85] The relationship of skin sensitiveness and

anaphylaxis was claimed by Landsteiner and Jacobs,[75] who produced anaphylaxis through the injection of picryl-chloride conjugates into guinea pigs previously rendered skin-sensitive to the uncombined chemical.

To what extent the above findings can be applied in explanation of the chemical and immunological processes involved in the production of contact dermatitis may be ascertained by a careful analysis of the discussion by Landsteiner himself.[91] He stated that, while conjugation of protein with nitro-substituted benzenes, with acyl chloride, acid anhydrides, and benzyl chloride, substances which are readily conjugated *in vitro*, helped to explain chemical sensitization, it was more difficult to give suitable explanation in the case of such other common allergenic drugs as picric acid, quinine, resorcin, *etc.* He stated, further, that more direct information had accrued from experiments on sensitization with simple chemicals alone, such as primrose extract, orthoform, p-phenylenediamin, mesotan, poison ivy, nitrosodimethylaniline, dinitrochlorobenzene, and others.

Landsteiner likewise contended that, while it seemed logical that results were the same whether the simple incitants or protein conjugates were employed for sensitization, this expectation was not entirely fulfilled. Thus, guinea pigs sensitized intracutaneously with an acyl chloride or picryl chloride reacted with skin inflammation to superficial application of the simple substances and with anaphylactic shock upon intravenous injection of acylated or picrylated protein. Intraperitoneal or cutaneous injection of picrylated stromata, on the other hand, produced anaphylaxis but, at best, very weak skin reactivity to contact. This showed, according to the author, that the two methods were not equivalent and that anaphylaxis and skin allergy to superficial application were two distinct forms of hypersensitiveness.

Further differences, noted by the author, between contact dermatitis and anaphylaxis were that in contact dermatitis there was no transfer by serum, desensitization was not readily accomplished, and, for producing sensitization, treatment of the skin with the simple excitant was far superior to other routes, which in general were of no avail. On the other hand, in common immunization, the resultant effect from treatment of the skin was generally far less pronounced.

In a final interpretation, however, Landsteiner felt that in principle the gap had been bridged as to whether skin sensitization was possible by way of the skin alone or by other routes. Guinea pigs previously treated with killed tubercle bacilli as adjuvants (to aid sensitization) were injected intraperitoneally with conjugates of picryl chloride and red cell stromata, thus achieving a high degree of skin sensitivity, as manifested by surface tests with the excitant (Landsteiner and Chase[32]). From this experiment, the author maintained that skin hypersensitiveness of the contact dermatitis type was engendered by a full antigen and hardly permitted any conclusion other than that this form of allergy was intrinsically related to typical immunization processes.

Considerable discussion has thus been devoted under the last two headings to a presentation of the hypothesis of sensitization by conjugation of simple

chemicals. To what extent this postulate can be applied to the manifestations of contact dermatitis in humans must be left to further investigators in this field. It would appear that the mechanism by which a considerable number of excitants are able to evoke contact allergic responses in man cannot be satisfactorily explained by the above evidence.

Another attribute of chemical compounds in relation to immunological reactions, namely, stereoisomerism, or the spatial structure of chemicals, was likewise studied. Landsteiner and Van der Scheer[93] demonstrated the significance of steric isomerism for the specificity of natural antigens. Employing antigens containing the acyl radicals of the three isomers of tartaric acid, the authors obtained immune sera by which it was possible to differentiate, sharply, optically isomeric compounds attached to the chemicals. Several other experimental and clinical studies pertaining to isomerism in chemical specificity can be mentioned briefly: Dawson and Garbade[94] on drug sensitivity to the alkaloids of quinine; Mitchell[95] on dermatitis to resorcin; Rothman, Orland, and Flesch[96] on procaine dermatitis; and Rostenberg and Kanof[97] on active sensitization with halogen substituted compounds of dinitrochlorobenzene. Another study in point is that of Pauling, Campbell, and Pressman,[98] who demonstrated the greater antigenic effectiveness of para-substituted compounds in comparison to meta- and ortho-compounds in general serological immune reactions. In some of the investigations on contact allergy of the skin, the greater effectiveness of the para-compounds in evoking sensitization was referred to.

In summary, it was demonstrated by the above studies that certain chemicals of known simple constitution were rendered capable of becoming effective sensitizing agents by virtue of their ability to form conjugate compounds with proteins or of the spatial relationship of their component parts (steric isomerism).

Summary

The subject, contact dermatitis, was defined and classified. Factors involved in the mechanism of the development of sensitization were discussed, namely: the sensitizing substance; the role of exposure to the excitant; techniques employed to induce sensitivity; the experimental animal; the flare-up phenomenon; incubation period; sensitization by patch test; susceptibility of subjects; and the state of permeability of the sensitized skin. Experiments which attempted to explain the manner in which sensitization spread from the original site of exposure were described. Finally, the immunology of contact dermatitis and its possible relation to the more recent studies in chemical specificity were presented.

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ATOPIC ALLERGY: REAGINIC SENSITIVITY

By Matthew Walzer

Jewish Hospital, Brooklyn, New York

Atopy, a noncommittal term meaning "strange illness," was originally introduced by Coca and Cooke[1] in 1923 in a theoretical classification of the various forms of hypersensitiveness. It was intended for those forms of human hypersensitiveness, particularly asthma and hay fever, which had been shown to be subject to hereditary influence. The nature of the immunologic mechanism in these conditions was still unknown at the time, but the presence of hypersensitiveness could be detected by skin tests with antigens which produced immediate transient whealing reactions.

In a recent discussion of the origin of the term atopy, Cooke[2] stated: "At that time it was thought that the immediate wheal-reacting allergies and the hereditary group, so-called, were one and the same. Later studies showed that infective or bacterial asthma is likewise and equally subject to the hereditary influence, but does not carry the skin-reacting factor. Today 'atopy' is often used also to designate allergies of the skin-reacting type rather than those with an hereditary factor, and this has caused much misunderstanding."

Coca[3] has always stressed the hereditary implication of the term atopy. Although he and Grove[4] pioneered in investigating the skin-sensitizing antibody, which they named "the atopic reagin," he did not make the positive skin reaction which is mediated by this antibody a prerequisite for application of the term atopy.

Coca now finds his original definition of atopy inadequate in that its designation as "a group of allergic diseases that are subject to common hereditary influence" does not distinguish it from idioblapsis, another category of familial allergic disease which he[5] has more recently reported. Since the mechanism of idioblapsis is not based upon a demonstrable antibody and atopy does commonly manifest the atopic reagin, he offers this feature as a distinguishing characteristic between the two hereditary allergic groups. He therefore modifies his original definition of atopy to read "a group of allergic diseases that are subject to a common hereditary influence and in which the atopic reagins are often demonstrable." Coca has, however, repeatedly pointed out that heredity exercises its influence in various ways on the atopic shock tissue, independently of the reaginic factor, and that it is possible for an atopic shock tissue to be activated by immunologic mechanisms in which reagins play no part. In fact, it is even possible for the atopic shock tissue to be aroused nonspecifically.

It is unfortunate that students in the field of allergy have, for the most part, focused their interest on the skin-sensitizing antibody, while the shock tissue in atopy has received scant attention. Few have grasped the full significance of the fact that, in the absence of a functioning shock tissue, the reagin loses most of its power to mediate allergic symptoms. On the other hand, the shock tissue *can* operate in the absence of demonstrable reagins. Hence, it is important to bear in mind that, while reaginic hyper-

sensitiveness is an outstanding characteristic of atopy, it is by no means a constant feature nor is it the only mechanism involved. The hereditary transmission in atopy applies to tissue predisposition as well as to immunologic tendencies. In other words, atopy and reaginic hypersensitiveness are not synonymous.

The original characterization of atopy as a form of human hypersensitiveness is now obsolete, in view of the demonstration of this mechanism in several species of animals.[6]

There are illnesses other than hay fever and asthma which fall into the category of atopy. Their inclusion is based on their unusually high incidence in patients with asthma or hay fever, either as associated or past illnesses or in their family histories. Most common is the food eczema of infancy and childhood, now commonly known as atopic dermatitis, which is a frequent forerunner or associate of asthma and hay fever and in which the atopic reagin is commonly demonstrated. Perennial allergic rhinitis or vasomotor rhinitis is another common expression of the atopic tendency. Urticaria, angioneurotic edema, and migraine are slightly less frequent but quite common manifestations. In most of these conditions, despite obvious clinical sensitivities, positive skin reactions are usually lacking. It would be difficult, however, to exclude many of these cases from the atopic group solely on this basis. Less typical manifestations of atopy include headache, gastrointestinal disturbances, pruritus, cough, and other symptoms.

Asthma and hay fever each affect approximately from 1.5 to 2 per cent of the population of this country. With the inclusion of the other expressions of atopy, the incidence of the whole group of illnesses is usually estimated at about 7.5 to 10 per cent of the population.

Asthma and hay fever seem to occur with greater frequency among Caucasians than among the other branches of the human family.

Most of the comprehensive studies on the sex distribution of atopic illnesses seem to indicate that there is a slightly higher incidence among males up to the age of puberty and that there is a greater incidence among females thereafter.

The onset of atopic symptoms occurs more frequently in the first decade of life than in any other. Food sensitivities are the earliest to appear, and most frequently they express themselves as eczema or disturbances of the digestive or respiratory tracts. Inhalant sensitivites tend to appear later and to manifest themselves in respiratory illnesses. Most food sensitivities of mild or moderate intensity, starting in infancy or early childhood, tend to disappear spontaneously in the course of a few years. Severe sensitivities to certain food allergens may persist for one or two decades or even longer. Sensitivities to inhalants tend to run a more protracted course than do sensitivities to foods. However, these statements are generalizations. Food and inhalant allergies may appear at all ages in atopic individuals and may run varied and unpredictable courses. Hay fever tends to appear at a somewhat later date than do most of the other reaginic atopic conditions. Its onset is most frequent in the second or third decade. But allergic rhinitis, caused by sensitivities to foods and to inhalants exclusive

of pollens, tends to occur as early as asthma, the onset of which is greatest in the first decade of life.

Atopy has no pathognomic symptomatology or pathology. Conditions simulating atopic illnesses frequently occur in nonatopic individuals. The diagnosis of an atopic illness therefore depends upon the recognition by the clinician of many of the common features of atopy. They include: (1) the more or less classical clinical expressions of the atopic state; (2) the hereditary nature of the illness, expressing its effects, as will be noted presently, in several ways; (3) the pronounced tendency to develop hypersensitiveness, of which the most outstanding and characteristic form is the reaginic type; (4) the prominence of transient localized edema as a finding in most forms of atopic illness; (5) the presence of an excess of eosinophilic leucocytes in the blood and the tendency toward the deposit of these cells at the site of the atopic reaction and in the secretions of the affected mucous membranes; (6) the absence of pathognomic tissue changes on microscopic examination (the edema and tissue eosinophilia being only transitional and completely reversible phases of the reaction and by no means specific for atopic illness); (7) the tendency toward chronicity and recurrence of symptoms; and (8) the relatively benign course of these illnesses, which, in proportion to their chronicity, inflict surprisingly little permanent damage on the affected organs.

Many factors have interfered with the proper performance of statistical studies on the inheritance of atopic illnesses. Despite these handicaps, sufficient evidence has been accumulated to establish, beyond a doubt, the importance of heredity as an etiologic factor in these conditions. The pioneer studies of Cooke, Vander Veer, and Spain,[7, 8] as well as subsequent contributions of other workers, have shown that the influence of heredity expresses itself in several ways.

First, heredity influences the number of offspring to be affected by atopic illnesses. Whereas the incidence of positive family histories among normal individuals has generally been reported to be in the neighbourhood of 7 per cent, it is much higher among atopic patients. The average incidence of positive family histories in a number of series of atopic adults was found to be about 49 per cent. In studies on atopic children, positive family histories occurred in approximately 58 per cent. The number of offspring affected is definitely greater when the hereditary influence is bilateral than when it is unilateral.

Second, heredity exercises its influence upon the age of onset of atopic symptoms. This fact, originally presented in Cooke's[8] studies, has been repeatedly confirmed by subsequent workers. The majority of children with a bilateral atopic inheritance have already manifested their predisposition clinically by the age of ten. During this same period, symptoms appeared in only about half as many children with unilateral family histories, the maximum incidence of onset in this group occurring between the tenth and fifteenth year. In patients with negative family histories, the highest incidence is not reached until about the thirtieth year.

Third, the localization of symptoms and the organs affected are, to a

minor degree, influenced by heredity. Clarke, Donnally, and Coca[9] called attention to the fact that, among atopic patients whose sole complaint was hay fever, the antecedent history for hay fever as a sole expression of the atopic tendency was much higher than that for asthma. Among pure asthmatics, the excess of pure asthma over pure hay fever in the antecedent history was even more pronounced. There are, however, so many exceptions to this general tendency that this expression of hereditary influence does not appear to be so important as those previously mentioned.

Fourth, the atopic individual inherits a predisposition toward reagin production following *casual* and *not unusual* contact with allergens (or atopens, as they are called when used in relation to atopy) which possess no striking antigenic properties. Once initiated, this reaginogenic activity may continue indefinitely, long after antigenic excitation has ceased. The allergens for which reagins are produced are different in parent and offspring, indicating that the *predisposition* to become sensitive, *not* the specific sensitivity, is transmitted. Not all atopic subjects manifest this reagin-forming characteristic. In hay fever, reagins for the offending pollen are almost always demonstrable. In nonseasonal allergic rhinitis, in perennial asthma, and in atopic dermatitis, not more than 60 per cent of patients have reagins. In the remainder, activation of the atopic shock tissues, occurs, directly or indirectly, as a result of nonreaginic allergies, infection, trauma, endocrine dyscrasias, organic pathology, psychosomatic disturbances, physical allergies, chemical irritations, and other processes.

Fifth, there is the inheritance in the atopic individual of what is called, for want of a better term, "predisposed shock tissues," which tend to respond to varied types of excitation with the typical clinical expressions of atopy. Since the tendency to develop atopic symptoms is transmitted much more regularly than the tendency to develop reagins or even to manifest sensitivity, the preeminent importance of the shock tissue as an hereditary factor in the mechanism of atopy is obvious.

The mode of transmission of atopic disease is debatable and promises to remain so for some time. Data on this point will not be trustworthy until all of the possible manifestations of atopy are established, until their actual presence in the patient is recognized, and until two or more generations of many large atopic families are carefully studied.

Hay fever or pollinosis represents an expression of the atopic state which is particularly suitable for study. It is probably the commonest and most readily recognized atopic illness. The offending allergen is a pollen, almost always identifiable by skin tests, the results of which may be corroborated by correlation with the clinical history. In most patients, contact with the offending pollen is unavoidable, and treatment by injections of gradually increasing doses of the offending pollen becomes necessary. For these reasons, the immunologic mechanisms involved in hay fever have been investigated more extensively than those in other atopic illnesses.

Despite the fact that the skin does not participate in the symptomatology of hay fever, the diagnosis in this illness may routinely be made by skin testing, a relatively simple technique in comparison to the more involved

procedure of testing the mucous membranes, which are the seat of the allergic reaction. Skin testing[10] for atopic hypersensitiveness is usually performed either by the scratch or the intracutaneous method or by some modification of these two basic techniques. In the scratch method of testing, introduced by Schloss[11] in 1912, the allergen is gently rubbed into a superficial scratch in the skin. In hay fever, tests are made with pollens, but in other conditions a wide variety of foods, inhalants, or other allergens may be used. In the intracutaneous technique introduced by Cooke,[7] minute amounts of sterile extracts of allergens are injected into the skin. With both techniques, positive reactions consist of wheals, usually irregular in outline, with a tendency to pseudopod formation. The wheal is usually surrounded by an erythema and accompanied by itching. Positive reactions start to develop within a few minutes, reach their height in about ten to fifteen minutes, and disappear in about an hour. For diagnostic purposes, either or both of the techniques are commonly employed, depending upon the preference of the clinician and the nature of the problem. In the hands of the novice, the scratch technique is the safer method of testing. The intracutaneous technique is more effective in diagnosis, but requires greater experience and care, because antigens are actually introduced into the body with this procedure. For research purposes the intracutaneous test has proved the more adaptable and effective technique.

Both methods of testing are based upon the same immunologic mechanism, first experimentally demonstrated by Prausnitz and Küstner[12] in 1921. Küstner was clinically sensitive to fish and manifested a marked positive reaction on skin test with this allergen. The introduction of a small amount of Küstner's serum into Prausnitz's skin resulted in a localized sensitization to fish at the injected site. This was proved experimentally by an intracutaneous test with the fish allergen the following day. This skin-sensitizing property was shown by Coca and Grove[4] to be more or less typical of sera obtained from atopic patients who showed positive skin reactions to the common atopens. Because the sensitizing substance contained in these sera manifested properties which differed decidedly from those manifested by the sensitizing antibody in anaphylaxis, the term "atopic reagin" was suggested for it.

The tissue-sensitizing property represents virtually the only one by which the atopic reagin may be detected and identified. Hence, almost all studies of this antibody involve, at some point, direct skin testing of the patient or the use of the Prausnitz-Küstner technique or some modification thereof.

It has been experimentally demonstrated that sensitization of tissue cells starts within a few minutes after the introduction of the reagin-bearing serum into the skin and is completed within a few hours. This induced local sensitivity starts to decline gradually after a week or so, but, with high-titered sera, evidences of sensitivity may persist for as long as eight or ten weeks after sensitization.

The intensity of sensitization induced at a site depends, to a considerable degree, on the reagin concentration of the serum. In untreated patients with hay fever, Levine and Coca[13] found a definite proportional relationship

between the degree of the patient's cutaneous sensitivity and the reaginic titer of his blood. This is not regularly true in cases of asthma and other atopic illnesses.[14]

Not all individuals accept passive sensitization to the same degree. Generally speaking, atopic subjects are less receptive to passive local sensitization than are nonatopics.[15] The factors responsible for these variations in receptivity are unknown. Mucous membranes may also be passively locally sensitized by intramucosal injections of reaginic sera.[16]

For the testing of passively sensitized skin sites, about 0.02 ml. of allergenic extract is injected intracutaneously, as superficially as possible. The trauma produced by the sensitizing injection of serum temporarily diminishes the responsiveness of the skin site. For this reason, the test is best performed after an interval of three or four days.[3a] A positive reaction consists of a wheal or an erythema, usually both, which are not obtained with a control test performed on an unsensitized site. This opportunity to compare similar tests on sensitized and unsensitized sites represents the greatest advantage of passive transfer testing. No similar control is afforded in direct testing on the patient.

A marked positive passive transfer reaction affects the sensitized cutaneous site in several ways.[17] It impairs the whealing response of the tissue to any type of subsequent test for from one to four weeks. In addition, the positive reaction injures *all* the reagins remaining at the site, including those not related to the antigen. Hence, one marked reaction at a sensitized site materially reduces the value of all subsequent testing at that site. The stronger the reaction, the less reliable are the results of subsequent retests of the site. The failure to realize this simple fact has resulted in reports of bizarre findings in experiments in which the passive transfer technique or its modifications were employed.

The atopic reagin possesses properties which differ, in many respects, from those of the anaphylactic or precipitin antibody. The latter, while playing an important role in animal hypersensitiveness, is of limited significance in human allergy. A comparison[3b] of the two types of antibodies reveals the following points of differentiation.

(*1*) The atopic reagin is decidedly more susceptible to heat than the precipitin. By heating serum at 56°C for an hour, it is possible to eliminate its reagin activity. Such treatment does not seriously affect precipitin antibodies.

(*2*) The atopic reagin totally lacks the power of sensitizing guinea-pig smooth muscle, a cardinal characteristic of the anaphylactic antibody. The latter, on the other hand, manifests little of the human skin-sensitizing property so characteristic of the atopic reagin.

(*3*) Mixtures of reaginic serum and related antigen yield no visible precipitates, such as are produced in the proper mixtures of anaphylactic antibodies with their respective antigens.

(*4*) Fixation of complement by mixtures of reaginic serum and antigen occurs irregularly and only with selected sera.[18] It is transient in comparison to the readily demonstrable, more permanent fixation which occurs with

mixtures of precipitin and antigen. Moreover, the zone of antigen dilution in which this phenomenon occurs is different for the two types of antibodies. The reaginic reaction is operative in zones of much higher antigen dilution than the precipitin reaction.

(5) Compared to the strong affinity existing between the anaphylactic antibody and its related antigen, the attachment between unanchored reagin and its antigen is an extremely loose one and is reversible to an unusual degree.

A twenty-four-hour mixture of reagin and related antigen in the proper dilutions, when introduced into the skin, produces, within twenty minutes, a specific positive reaction, indicating that there has been an attachment of reagin to tissue cells even in the presence of an excess of antigen. The sensitized cells are then acted upon by the antigen, resulting in wheal formation and complete or partial loss of site sensitivity. So slight is the loss of antigenic power in the test tube mixture and so striking is the positive reaction resulting from its intracutaneous introduction that some workers have denied the occurrence of any *in vitro* reaction and have maintained that all neutralization of reagin occurs *after* the introduction of the mixture into the skin. This seems unlikely, since Bowman has found that twenty-four-hour mixtures of reagin and antigen produce smaller immediate reactions in the normal skin than do those mixtures prepared just before injection. The fact that fixation of complement has been demonstrated with reaginic sera also supports the belief that some antigen-reagin reaction takes place *in vitro*, even though the combination is weak and is, to a large degree, reversible.

Reagin production is not readily induced experimentally with the food and inhalant antigens, which are the common excitants of atopic symptoms. Even in atopic subjects, who would be naturally predisposed to form reagins, Brunner[19] failed, with one questionable exception, to stimulate their production by repeated subcutaneous injection of large amounts of egg white, rabbit epithelium, and orris root, all common clinical atopens.

With *Ascaris lumbricoides* antigen, which possesses unusual antigenic properties, Fülleborn,[20] Brunner,[19] and others showed that reagin formation could be readily induced in nonatopics as well as in atopics by relatively few skin-test doses of the extract.

In an attempt to study some of the factors which might influence reagin production, a series of studies on sensitization to *Ascaris* in humans was undertaken by Davidson, Kailin, and co-workers.[21] Five groups of subjects, among whom none showed positive skin reactions to *Ascaris*, were studied successively. Skin-test doses of *Ascaris* were administered at weekly intervals until an immediate positive skin reaction developed to the test, at which time reagins could be demonstrated in the blood by passive transfer test. About 19 per cent of the subjects developed immediate positive reactions to Ascaris at the time of their third weekly skin-test dose, which was fourteen days after their first contact with the antigen. About 54 per cent were sensitive by the twenty-eighth day and about 92 per cent by the seventy-seventh day. The rate of reagin formation to was *Ascaris* definitely

faster in the Negro than in the white race. There was suggestive evidence that males were more readily sensitized to than *Ascaris* females. Chronic tubercular infection did not appear to be a factor influencing the rate of sensitization. Among adults, age was not a factor. The rate of sensitization in any group could not be correlated with the natural incidence of positive reactors resulting from parasitic infestation in that population group. The artificially induced reagins to *Ascaris* persisted for more than six months after sensitization in more than half the cases tested, with a tendency to longer duration in the Negroes.

It is impossible to state, at this time, whether the race and possibly the sex factors which seemed to influence artificial sensitization with *Ascaris* allergen will be found to apply to reagin formation with the common excitants of atopic illnesses. Reagins stimulated by nonparasitic antigens may appear in normals as well as in atopics following parenteral injection of immune animal sera, insulin, liver extract, and other products of animal origin, but their production is irregular and unpredictable.

It is apparent, therefore, that atopic reagins are not pathognomic of atopic illnesses. There is, nevertheless, the striking tendency exhibited by the atopic individual to become sensitive to common atopens possessing no unusual antigenic properties in animals and to stay sensitive, frequently for years after contact with the excitant has been discontinued. It is this predilection to reagin formation which facilitates the diagnosis of the atopic hypersensitive state by means of skin testing.

Unfortunately, the presence of the skin-sensitizing antibody and the positive skin reaction which it mediates are not an absolute index of the patient's clinical sensitivity to the particular atopen in question. While a positive skin reaction to an atopen usually may be correlated with an active sensitivity to it, the reaction frequently bears no obvious relationship to symptomatology. The reaction may be a forerunner of clinical sensitivity or the residual evidence of a previous sensitivity. This lack of correlation may be attributable in part to the patient's failure to contact the atopen in its active state, or through natural channels, or in sufficient concentration to be effective. In addition, there are inactive or anergic states of the shock tissue which render it insusceptible to excitation by the immunologic mechanism. Such anergic states may occur spontaneously or follow specific treatment. They are also frequently produced nonspecifically by various forms of therapy or by fever, infections, pregnancy, and severe tissue damage, such as fractures or surgical procedures. Hence, positive reactions, even though they are specific, need careful interpretation.

No less important is the evaluation of negative reactions. Frequently in tests with foods and quite regularly with drugs, the skin reaction is negative, although clinical sensitivity to these substances is pronounced. It is obvious that there is more to the art of specific diagnosis in atopic illness than the mechanical performance of the skin test.

In addition to its importance in the direct testing of patients, the skin-sensitizing power of the atopic reagin has been employed for diagnostic and experimental purposes in many other ways. From the practical point of

view, it is being employed for the indirect testing[3c] of atopic patients in whom direct testing is inconvenient or impracticable. By sensitizing many skin sites on the arms of a normal subject with small amounts of the patient's sterile serum, it is possible to test these areas, after an interval of a few days, with those allergens with which the patient would ordinarily be tested.

Another use of passive local sensitization has been in studies of antigenic absorption.[22] A cutaneous site, sensitized with a reaginic serum of high titre, will react violently, within five minutes to an hour, following the oral administration of the related antigen, and the entrance of minute traces thereof into the circulation. With this technique, it has been possible to demonstrate the presence of traces of unaltered antigen in the circulation, following its application to practically all mucous membranes, serous surfaces, and even to the skin.

Passive sensitization of human mucous membranes has been employed in studies of reaginic reactions in these tissues. Among the most interesting of these was the allergic reaction of the passively sensitized ileum and colon.[16]

From the investigative point of view, attempts at passive sensitization of the common laboratory animals with human reaginic sera were uniformly disappointing until Caulfeild and Straus almost simultaneously reported success with the Rhesus monkey. The skin and mucous membranes of this animal are readily sensitized with human sera of high titre, and this has afforded an opportunity for many unusual types of investigation. Of singular interest has been the study of allergic reactions in the abdominal organs of the monkey.[23]

Man accepts passive cutaneous sensitization with the sera of some animals. However, the intracutaneous injection of these heterologous sera is usually followed by rather marked inflammatory reactions which render the skin sites useless for purposes of testing. Hence, relatively little has been learned from the experimental use of reagin-bearing animal sera in man.

In anaphylactic shock in the guinea pig, rabbit, and dog, the seat of the reaction is constant and characteristic for each animal species. The atopic reaction in humans involves no such characteristic shock organ. In animal anaphylaxis, the role of smooth muscle as the shock tissue is readily demonstrable with the Schultz-Dale technique, employing the excised smooth muscle strip of the uterus or intestines. No similar evidence implicating human smooth muscle has yet been presented. Tuft[24] obtained a human uterine muscle segment from a patient who had been sensitized and showed a positive skin reaction to horse serum. Atopic reagins to horse serum were present in her circulation. Tests of this muscle strip with the Schultz-Dale technique yielded no specific contractions to horse serum.

Attempts to sensitize the smooth muscle of laboratory animals with human reaginic sera have consistently failed. Even in the Rhesus monkey, the best animal receptor of sensitization with human reagins, Albert[25] could find no fixation of reagins in the smooth muscle of the intestinal strip, although large amounts of potent reaginic sera were employed for sensitization. There was, likewise, no fixation of the anaphylactic antibody by the smooth muscle in this animal.

Despite these consistently negative findings, there has been considerable reluctance, in some quarters, to relinquish the hypothesis that smooth muscle is the seat of the immunologic reaction in atopic illnesses. In support of this concept, the bronchial spasm in asthma and the spasm of the bowel in gastrointestinal allergy are offered as evidence. But, here again the experimental proof that the immunologic reaction actually takes place in the smooth muscle is lacking. Not even the smooth muscles in the blood vessels of sensitive mucous membrane contract during the atopic reaction. In slit lamp studies of positive ophthalmic reactions induced with pollens in hay fever patients, Feldman and Sherman[26] observed only vascular dilatation during all phases of the specific response.

Further evidence against smooth muscle as the shock tissue in gastrointestinal allergy is found in the roentgenographic studies by Fries and Zizmor.[27] After a barium meal containing a specific allergenic offender, the characteristic response of the allergic stomach consisted of a marked loss of tonicity and a pronounced decrease in peristalsis, resulting in a long delay in emptying of the organ. In the allergic intestines, spasm was the more typical finding, but dilatation was by no means an uncommon occurrence. The fact that the smooth muscle relaxes regularly in the allergic reaction of the human stomach, and occasionally in that of the bowel, eliminates it as the shock tissue in these phenomena, since Schultz-Dale studies reveal that smooth muscle strips of sensitive animals invariably contract in response to antigenic contact. Any muscular contractions which occur in bronchial asthma or gastrointestinal allergy are, therefore, secondary responses to the allergic reaction which occurs in the neighboring mucous membranes or other tissues.

The exact site of the immunologic reaction in atopic hypersensitiveness is still a matter of conjecture. While the particular type of cells affected in humans may be constant, the organs in which these reactions occur vary widely, much more so than in laboratory animals. Even in the same individual there is frequently a tendency for alternation in the involvement of shock organs. The eczema of infancy and childhood commonly gives way to some other atopic manifestation, such as asthma or hay fever, in later life. Occasionally, two atopic symptoms, such as asthma and eczema, may alternate several times in the life of the same individual. The factors responsible for these variations in susceptibility of the shock tissues are still obscure.

There is also little known concerning the factors which are responsible for the particular pattern of sensitivities which each patient develops. There is evidence to suggest that the development of sensitivity to an atopen is not accidental. The absorption into the circulation of unaltered food and inhalant allergens has been shown to be a normal physiologic phenomenon occurring throughout life in atopic and nonatopic subjects alike.[22] With variable amounts of allergens constantly reaching the circulation by way of the digestive and respiratory tracts, an explanation for the establishment of sensitivity on the basis of accidental excessive absorption of a particular antigen becomes untenable.

The tendency, commonly manifested by atopic patients, to develop multiple sensitivities to certain types of antigens, with the allergenic pattern varying for each individual, speaks for a selectivity in sensitization, probably the result of some predisposition. From the studies of Harten and Bowman,[28] one is led to the conclusion that, among patients with clinical manifestations of hay fever, there is a pronounced tendency to develop reagins, though to a variable degree, to the strong pollen excitants to which they are exposed. Such a predisposition to sensitization to allergens of a particular type is commonly observed in patients sensitive to animal danders, fish, cereals, legumes, meats, *etc.*

The importance of antigenic contact as a prerequisite to reagin formation was brought out in the early studies of Grove,[3d] who reported complete absence of sensitivity to ragweed, the most important American pollen excitant, in hay fever patients in Germany, where that plant does not grow. Similarly, Algeroba pollen, the most important offender in Hawaii, gave uniformly negative reactions in hay fever patient in New York, where the plant does not exist.

One must regard with suspicion reports of reagin formation without previous contact with an antigen. In such cases, it is likely that contact has occurred, but in a manner not recognized or remembered by the patient. There is the additional possibility of a previous contact with an antigen closely related to the one in question and possessing decisive antigenic components in common with it.

Passive sensitization of the fetus, *in utero*, a phenomenon readily demonstrable in guinea pigs, does not occur in humans. Bell and Eriksson's[29] report that maternal reagins, unlike other antibodies, do not pass through the placenta into the fetal circulation has been repeatedly confirmed. No one has demonstrated the presence of atopic reagins of any sort in the newborn. Even when reaginic formation and cutaneous sensitivity were actively induced with *Ascaris* antigen in pregnant women, Zohn[30] could find no trace of atopic reagins in the cord blood at birth.

Proof is still lacking for the hypothesis that active intra-uterine sensitization occurs in humans, as it does in guinea pigs, as a result of contamination of the fetal blood by antigen from the maternal circulation. In such a case, it would be necessary to demonstrate the presence of atopic reagins at birth or during the first two or three months of life. In the latter instance, it would be necessary to establish a complete absence of contact with antigen after birth. Since Donnally[31] and also Brunner[32] demonstrated the excretion of unaltered food allergens into the mother's milk, it would be necessary to exclude this source of antigenic contact between birth and the appearance of sensitization.

The role of histamine in various allergic reactions has already been discussed and needs receive only brief consideration here. The exhaustive experiments of Lewis[33] and his co-workers revealed a marked resemblance between the characteristics of the immediate cutaneous whealing reactions induced by pricking the skin with histamine and with a specific allergenic excitant. This led Lewis to conclude that the action of the antigen upon

the specifically sensitive tissue cells resulted in the liberation of a substance which exhibited a marked similarity to histamine. This histamine-like substance, which Lewis termed H-substance, was said to damage the minute skin vessels, causing an increase in their permeability. The Lewis theory probably suffers from oversimplification, in that it fails to account for many experimental phenomena noted by other investigators in this field. In our own experience,[34] the histamine theory fails to account for the dissimilar conditions of responsiveness which prevail at the sites of histamine and specific wheals produced on the same atopic individual. For many days after the initial excitation, the site of a histamine wheal shows a diminished responsiveness to restimulation with histamine. The specific wheal, on the contrary, leaves its site with an increased responsiveness to restimulation, not only with the specific excitant but also with histamine. There is also the curious fact that identical histamine skin tests injected along the arm produce wheals of gradually increasing size as one proceeds downward, while specific tests with atopens behave in the opposite manner.[35] There is the additional finding, determined by electrophoretic studies,[36] that successful specific treatment of hay fever patients with pollens does not alter the threshold of their cutaneous responses to histamine. It is difficult to reconcile these findings with the histamine theory proposed by Lewis.

Attempts to approach the treatment of atopic illnesses by immunization against histamine in one form or another have, on the whole, been disappointing. Histamine injections have proved of limited value in cases with reaginic sensitivity. Immunization with histamine-azo-protein, employed in the hope of stimulating antibody formation against the hapten, histamine, such as Fell[37] claimed to have produced in rabbits, has failed to yield beneficial results. The use of histaminase, aimed at the enzymatic destruction of histamine *in vivo*, is theoretically unsound and has proved to be valueless clinically.

The antigenic substances or atopens which are the specific excitants of atopic reactions are diverse in nature. The identity and chemical nature of the excitant is still uncertain in many of the most important allergens, including such prevalent offenders as pollens and house dust. For this reason, little progress has been made in the methods of standardization of materials used for the testing and treatment of atopic illnesses. Many of the important atopens are proteins of a complex nature and of large molecular size. In the case of pollens, however, there is evidence to indicate that they are of comparatively small molecular size and that they manifest the properties of large-sized complex polypeptides.[38] Despite the fact that pollen is a relatively poor anaphylactogen, it is a potent and extremely important atopen.

In atopic sensitivity to drugs and chemicals, reagins are almost uniformly absent. Several notable exceptions to this rule have recently been reported. Feinberg[39] found evidences of reaginic sensitivity to drugs among workers in a factory where sulphonechloramides were prepared. The two most important offenders were chloramine T and halozone, simple chemical substances of low molecular weight (211). These drugs produced asthma and

allergic rhinitis in fourteen workers who had handled them for from six months to ten years before they developed symptoms. Most of the patients had positive personal or family histories of atopy and showed positive skin reactions to other atopens. In four of the six patients tested, marked passive transfers to chloramine T in high dilution were obtained. A case of reaginic sensitivity to a sulfonamide was recently reported by William Sherman, and reagins to phthalic anhydride were found in a chemist by Kern. In all of these cases, the patients showed immediate positive reactions to direct tests with the chemicals.

With rare exceptions, bacteria and bacterial products do not yield immediate positive skin reactions of a reaginic nature. Delayed skin reactions are likely to follow skin tests with bacterial allergens.

The treatment of atopic hypersensitiveness may be approached in several ways. Probably the simplest and most effective method is to eliminate contact, if possible, with the offending allergens. In most food allergies, this not only results in rapid clearing of symptoms, but, if continued long enough, is usually followed by a loss of sensitivity. The latter outcome is less easily achieved with inhalant sensitivity.

When exposure to the excitant can not be easily avoided, as is the case with most pollen-sensitive cases, treatment with the specific offender is indicated. When the pollinating season is already on, small daily intracutaneous doses of the pollen may alleviate symptoms. Preferable, however, is the preseasonal form of treatment involving subcutaneous administration at four- to seven-day intervals of gradually increasing doses of pollen, varied according to the patient's tolerance. The protective effect of dosage wears off rapidly, so that preseasonal treatment must be repeated each year, unless the patient continues treatment perennially, receiving his maximal dosage at four-week intervals indefinitely. The latter practice seems to offer the most satisfactory results. Hay fever treatment by the oral administration of pollen is theoretically unsound and disappointing in practice. All forms of "rush" treatment, which attempt to hasten or force dosage more rapidly than the patient's tolerance will permit, are hazardous and are generally discouraged.

The fact that specific treatment produces only partial and temporary benefit is further evidence that it does not desensitize the atopically sensitive human in the same sense that the anaphylactic guinea pig may be desensitized by proper doses of antigen. The treated patient who has obtained a satisfactory result tends to show no loss of reagins but may even exhibit a slight increase in the reagin titre of his serum. This finding, first reported by Levine and Coca[13] and repeatedly corroborated since, turned the quest for information on the mechanism of specific treatment in other directions.

Cooke[40] thought he had found the answer when he reported, in 1935, the detection of a so-called "blocking antibody" which appeared in the serum of hay fever patients as a result of treatment with pollen. Mixtures of pollen and post-treatment serum, when injected into normal skin, gave little or no immediate reactions, while mixtures made with pollen and ante-treatment

serum produced strong immediate positive reactions. These findings and the results obtained on retests of the injected sites led Cooke to believe that treatment had produced a new antibody which blocked the antigen-reagin reaction in the tissues. Subsequent studies[41] revealed that these antibodies were formed in nonsensitive nonatopic humans following a series of pollen injections. As he continued to study the problem, Cooke's[42] enthusiasm waned, until he eventually doubted that the blocking antibody was responsible for the clinical protection afforded by specific treatment.

Loveless,[43] who had collaborated with Cooke in his earlier studies, took a different view of the matter. In independent studies, she demonstrated that the antibody in the post-treatment serum is thermostable, in contrast to the reagin, which is quite susceptible to heat. She showed, furthermore, that thermostable antibody, in competing with reagin for the same antigen, was the more successful of the two in combining with and neutralizing the antigen. This accounted for the differences which Cooke had observed in the behavior of ante-treatment and post-treatment sera and which he had attributed to a blocking action of the antibody.

Loveless[44] confirmed the findings of Cooke, Rackemann, and others that there was no direct correlation between the absolute titer of the thermostable antibody resulting from treatment and the clinical improvement of the patient. She denied the importance of this objection, however, on the ground that she believed the increase in titer, necessary to produce improvement, varied with each patient.

Alexander and Johnston recently devised an original capillary tube precipitation technique involving tests with human sera, antigen, and immune rabbit serum, which provided another method of investigating this problem. Their first studies[45] seemed to indicate that relief of hay fever tended to correspond with the elevations in titer of the thermostable antibody. In their latest report on a large series of cases, however, these workers were not inclined to reaffirm their first impressions.

It seems likely that an alteration in the response of the shock tissue is the most important factor responsible for the clinical improvement induced by the treatment of hay fever. This is most effectively obtained by specific treatment in one form or another but, as previously noted, may be temporarily achieved even through nonspecific means. Just why or how the shock tissue in atopy becomes inactivated following treatment remains as much of a mystery as the reason for the spontaneous recovery from atopic illnesses even though the reaginic mechanism persists. These are among the major problems which today challenge the investigator in the field of atopic illnesses.

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ALLERGY OF INFECTION: RELATION TO IMMUNITY

By Beatrice Carrier Seegal

Department of Bacteriology, College of Physicians and Surgeons, Columbia University, New York

The accelerated vaccinia reaction or "disposition to sudden cuticular inflammation" was noted by Jenner[1] some 100 years before von Pirquet[2] reinvestigated the reaction as an example of an allergic condition. The term allergy had been introduced by von Pirquet[3] only one year previously. Thus a vivid description of hypersensitivity to an infectious agent preceded the present knowledge of allergic reactions by a full century.

Zinsser[4] has defined bacterial allergy as "a condition in which the body is sensitized to a bacterial antigen." This definition makes the problem seem disarmingly simple, although actually it is quite the contrary. In addition to producing all the known types of hypersensitive reactions, previously described under anaphylaxis, the products of infectious disease agents stimulate certain reactions which are generally peculiar to this type of allergen. Some, perhaps much, of the histopathology in chronic infection may be the result of allergic inflammation.

Two factors at least contribute to the varied manifestations of the allergy of infection. The first is related to the intricate structure of pathogenic microorganisms and their many biological activities which enable them to invade and excite inflammatory reaction. The second is a result of the host's response to infection. Experiments will be cited which indicate that the type of tissue in which the organism lodges and the reaction it evokes may influence the character of the allergic manifestations.

Anaphylactic Hypersensitivity Induced by Bacteria and Fractions of Bacteria. Studies made with whole microorganisms or with their fractions or products have shown that bacteria or their products may induce anaphylaxis in animals in a manner similar to cells or proteins of non-bacterial origin. Friedberger and Mita[5] described anaphylaxis induced by whole bacteria. Guinea pigs injected subcutaneously with suspensions of heat-killed *Vibrio metchnikovii* were fatally shocked 2 to 4 weeks later by intravenous injections of the same material. Recent observations with whole dead bacteria are those of Boldt, Tanner, Rosebury, and Kabat at Camp Detrick.[6] They found that subcutaneous injections of killed suspensions of *Brucella suis* or *Bacillus anthracis* sensitized guinea pigs so that symptoms of anaphylactic shock could be induced either by intravenous injection of the antigen or by exposing the animals to inhalation of clouds of the bacteria.

The first virus purified, crystalline tobacco mosaic virus, can sensitize the guinea pig so that anaphylactic shock follows the intravenous injection of the virus.[7] It has not been possible to demonstrate smooth muscle sensitivity by the Schultz-Dale technique in such animals.[8]

Whole bacteria may induce the Arthus type of sensitivity. Baker, Thomas, and Penick[9] sensitized rabbits by intracutaneous injection of living hemolytic streptococci. Subsequent intrapericardial injection of a heat-

killed culture of the same organism has resulted in extensive pericarditis and myocarditis similar to the Arthus reaction induced with soluble protein.

The phenomenon of passive anaphylaxis may be demonstrated with antiserum to whole bacteria or to bacterial fractions. Avery and Tillett[10] have passively sensitized guinea pigs with rabbit antipneumococcus serum and elicited fatal shock in these animals with the type specific carbohydrate. Lancefield[11] has studied the antigenic nature of fractions of the hemolytic streptococcus by this technique, using guinea pigs passively sensitized with rabbit antistreptococcus serums.

Another series of experiments has been designed to test the capacity of fractions of bacteria to produce allergic reactions in previously sensitized animals. For example, Enders[12] has utilized the "partial antigen" of the tubercle bacillus to induce anaphylactic shock in actively and passively sensitized guinea pigs. Mackenzie[13] has investigated anaphylactic sensitivity to pneumococcus filtrate. Guinea pigs received intraperitoneal injections of killed or living broth cultures of virulent pneumococci which produced active immunity. Anaphylactic shock might follow intravenous injection of a filtrate of the pneumococcus, and a positive Schultz-Dale uterine contraction was obtained when pneumococcus protein was added to the bath. Cutaneous allergic reactions were not obtained.

Fractions of bacteria may induce the Arthus reaction. Francis and Tillett[14] have reported that the specific capsular carbohydrates of pneumococcus Types I, II, or III, when injected intracutaneously in rabbits which had been immunized actively or passively to the whole organism, induced a delayed inflammatory response, the Arthus reaction. Zinsser[4] elicited what may be interpreted as a similar reaction by injecting pneumococcus autolysate into the joints of sensitized guinea pigs. Benacerraf and Kabat,[15] in their quantitative studies of the passive Arthus reaction in the guinea pig, have utilized horse antipneumococcus Type I serum to sensitize passively to the purified Type I polysaccharide.

It is possible both to sensitize and to shock with fractions of bacteria. For example, Sugg, Lurline, and Neill[16] have used diphtheria toxin and toxoid as anaphylactogens. Corper[17] has similarly demonstrated the anaphylactogenic activity of a protein from the tubercle bacillus.

It is interesting to observe that passive sensitivity with heterologous sera is not uniformly successful. For example, by the usual technique horse antipneumococcus serum will not passively sensitize the guinea pig so that anaphylactic shock results, following intravenous injection of the specific carbohydrate. Nevertheless, a local wheal and erythema reaction[18] or an Arthus reaction[15] can be demonstrated if the carbohydrate is injected intracutaneously. Francis and Tillett[14] have shown that, when a rabbit receives antipneumococcus horse serum and is subsequently tested by intracutaneous injection of the specific carbohydrate, a delayed type of reaction, characterized by edema, erythema, and sometimes purpura, follows.

Allergic Reactions Considered Characteristic of Infection. Allergic reactions following infection with the tubercle bacillus have been extensively investigated and constitute a classical example of bacterial allergy. The

intracutaneous injection of tuberculin in tuberculous animals produces the well-known tuberculin reaction, which, in time of appearance and duration, is similar to the Arthus reaction, the local inflammatory reaction which follows the subcutaneous injection of non-bacterial antigens in sensitive animals. The tuberculin reaction, however, though indurated, usually shows less gross edema and more hyperemia than the Arthus reaction. According to Rich[19] these two reactions differ in histopathology. The most unequivocal difference between them lies in the fact that the serum of the tuberculous animal cannot transfer the tuberculin reaction passively to a normal animal, whereas the passive transfer of the Arthus reaction with the serum of a sensitive animal is readily accomplished.

If tuberculin is injected in large amounts in tuberculous animals, focal and constitutional reactions occur and tuberculin shock and death may follow within a day or two. Like the tuberculin skin reaction, tuberculin shock is not transferable to a normal animal with the serum of a sensitive animal.

Tissue damage resulting from exposure of infected animals to tuberculin may be conveniently demonstrated by instillation of this allergen in the conjunctival sac. This has been practiced as a useful diagnostic test in cattle. Conjunctivitis is noticeable within a few hours, reaches its maximum intensity in 16–48 hours, and is severe, requiring almost a week to heal completely. Another type of tissue damage which may be readily demonstrated is inhibition of spermatogenesis following the intratesticular injection of tuberculin in sensitive animals.

In vitro, in tissue culture, the cells from tuberculin-sensitive guinea pigs and rabbits are prevented from migrating by the presence of an amount of tuberculin which is innocuous to the cells from a normal animal.[20] This hypersensitivity to the specific antigen is not found in tissue culture cells from animals sensitive to non-bacterial antigens.[21] Kirchheimer and Weiser[22] and Heilman and Feldman[23] have studied the correlation between cutaneous reactivity to tuberculin and sensitivity of tissue culture cells to the same allergen. The former workers found that the cells of splenic explants from guinea pigs desensitized to the intradermal tuberculin test were resistant to the cytotoxic action of tuberculin, when compared with cells from tuberculous, non-desensitized animals. Heilman and Feldman, using tissues from rabbits which had developed negative tuberculin reactions, due to overwhelming infection with the *Mycobacterium tuberculosis* or to intercurrent infections, found no corresponding resistance to tuberculin in their tissue cultures. Fremont-Smith and Favour[24] have extended *in vitro* studies of the cytotoxic effect of tuberculin to observations on bloods from human patients and have contrasted the behavior of these cells with those from mice and guinea pigs. They report an interesting difference in the behavior of lymphocytes and neutrophiles. The former, if from tuberculous man, mouse, or guinea pig, are lysed by tuberculin. The latter cells are lysed only if from man or guinea pig.

The results of the tissue-culture studies suggest that the antibody which reacts with tuberculin must be closely bound to the cells. This finds con-

firmation in the observation of Chase[25, 26] that the cells of tuberculin-sensitive guinea pigs are capable, when injected into normal animals, of passively sensitizing this host to tuberculin. Peritoneal exudates, spleens, lymph nodes, or blood from animals rendered hypersensitive by the injection of dead organisms provided the cells. Kirchheimer and Weiser[26A] have employed cells of guinea pigs sensitized by the injection of living cultures of the BCG strain of *Mycobacterium tuberculosis* and have obtained the same results.

In experimental studies of allergic phenomena resulting from inoculation with the streptococcus and pneumococcus, Andrewes, Derick, and Swift[27] and Julianelle and Morris[28] have reported an interesting spontaneous skin reaction called a "secondary" reaction. Rabbits were injected intradermally with certain strains of streptococci or pneumococci, either living or dead. After the primary injection of the bacteria, a small edematous and erythematous lesion developed, which healed within a week. When the spontaneous secondary reaction appeared, it came 8 to 10 days after the initial injection. It was characterized by the development of areas of edema and erythema at the old sites of inoculation, which sometimes became even larger than the original ones. Furthermore, ophthalmic sensitivity and a tuberculin-like shock could be demonstrated following the appropriate injection of the specific bacteria about two weeks after the beginning of the experiment.[29] Neither of these latter two reactions were transferable to a normal animal with the serum of a sensitive animal.

Another example of cell hypersensitivity, demonstrable *in vitro*, is furnished by splenic explants from guinea pigs suffering from a chronic Group C hemolytic streptococcus infection. Moen[30] exposed such tissue-culture preparations to filtrates of the infecting agent and demonstrated inhibition of migration and damage to the explanted hypersensitive cells.

Influence of the Host's Cellular Response on the Development of Bacterial Allergy. During infection there are a variety of cellular reactions on the part of the host to the invading bacteria. There is evidence from the work of Dienes and Schoenheit[31] that this cellular reaction may of itself influence the demonstrable allergic phenomena. They injected a fraction of a milligram of egg white into tuberculous lesions in rabbits or guinea pigs. Subsequent skin testing of these animals with the *egg white* resulted in a *tuberculin* type of skin reaction. The implication of the observation would seem to be that the cellular response to the infection by the tubercle bacillus influenced the development of allergy to the egg white so that it now behaved as a bacterial allergen. The same result was accomplished when the egg white was injected in a focus of infection produced by the vaccinia virus.

Recently the experiments of Dienes and Schoenheit have been extended by Raffel, Arnaud, Dukes, and Huang.[32] The latter group had made the observation that the injection in guinea pigs of a wax derived from the tubercle bacillus, together with proteins from this organism, established a tuberculin type of sensitivity to the proteins. When wax of the tubercle bacillus, together with egg albumin, was injected into guinea pigs and later

the animals were skin-tested with the egg albumin, a tuberculin-like reaction developed. Also, a delayed inflammatory response in the cornea followed the injection of the albumin in this site. These reactions were not demonstrable in animals sensitized with egg albumin alone. Bone-marrow cultures showed killing and lysis of cells by egg albumin when the explants were obtained from guinea pigs sensitized with the combination of wax and albumin.

The possible influence which focal lesions may exert on the character of bacterial allergy was illustrated in the experiments of Derick and Swift.[29] They tested for the ophthalmic reaction and the lethal tuberculin-like shock in rabbits which had received their initial inoculation of streptococci by a variety of routes. The intravenous route failed to promote either of these types of allergic reactions. On the other hand, primary inoculation into other areas, such as the knee, muscle, or peritoneal or pleural cavities, was followed, in a proportion of animals, by the development of such sensitivity. The authors conclude that it is probable, since this type of bacterial allergy seems to accompany the production of focal lesions, "that in these foci are produced the substances or conditions which lead to this type of bacterial allergy."

Summary: The Varieties of Bacterial Allergy. The experiments which have been described illustrate the following points: Infectious agents and their products may serve to produce anaphylactic shock, the Arthus reaction, and the Schultz-Dale reaction. In addition, infection with microorganisms, or injection of suitably chosen portions of these agents, may yield an allergic state which can be characterized by the induction of a tuberculin-like skin reaction, a delayed ophthalmic reaction, a tuberculin-like focal reaction, and, finally, delayed tuberculin-like shock. In contrast to the anaphylactic reactions, these latter cannot be transferred by the serum of the sensitive animal to normal animals. *Cells* of a tuberculous animal, however, are capable of passively sensitizing a normal animal. Tissue cultures of cells from infected animals may be inhibited in growth by extracts of the specific infectious agent. When a simple foreign protein, egg albumin, is injected into a focus of infection or together with a wax from the tubercle bacillus, it acquires many of the characteristics of a bacterial allergen.

Naturally Occurring Bacterial Allergy in Man. When the natural history of bacterial allergy in man is considered, it is desirable first to observe what evidence there is of an allergic response to bacteria in presumably normal, healthy individuals. Mackenzie and Hanger[33] have studied the development of sensitivity to filtrates of hemolytic and of viridans streptococci. Infants up to the age of ten months do not react to those filtrates. Thereafter, the percentage of positive reactions increases with age. It did not prove possible to correlate such reactions with known infections. Stevens and Jordani[34] have skin-tested asthmatics with nucleoproteins of *Staphylococcus aureus, Streptococcus hemolyticus, Neisseria catarrhalis, Haemophilus influenzae,* and *Streptococcus viridans.* Both the immediate wheal and erythema type of reaction and the delayed tuberculin-like reaction were ob-

tained. In six instances only did both types of reaction follow a single inoculation. Usually a patient, on repeated testing, reacted in the same manner to a given extract with either the immediate or the delayed type of reaction. A person might, however, give an immediate reaction to one extract and synchronously a delayed reaction to another extract. The intensity of the reactions fluctuated. The incidence of a tuberculin-like skin reaction to the nucleoproteins of the hemolytic streptococcus have been observed in infancy, childhood, and adult life by a number of investigators.[35] The reaction, rarely positive in infancy, becomes increasingly frequent with age. These observations illustrate the occurrence of allergic responses to organisms which may be carried in the upper respiratory tract.

Positive dermal reactions to products of the infectious agent have been demonstrated during or following many diseases caused by viruses, fungi, or parasitic helminths as well as by bacteria.[26] Such reactions may or may not be associated with immunity. For example, as a case of pneumonia approaches convalescence, a tuberculin-like skin reaction to the pneumococcus nucleoprotein is demonstrable and also a wheal and erythema type of reaction to the type specific soluble carbohydrate.[36] This latter reaction is associated with the development of immunity. Some allergic reactions presumably contribute to the pathology of infection. As stated by Zinsser,[4] "A body allergic to a given bacterial antigen is vulnerable to a degree that may lead to a serious pathological change." It is important to determine if these undesirable inflammatory reactions can be avoided and immunity preserved. This requires an examination of the relation of allergy to immunity.

Allergy and Immunity. The observation of Koch that a previously infected guinea pig, allergic to tuberculin, is capable of localizing and destroying reinjected tubercle bacilli has contributed largely to the point of view that allergy is necessary to immunity in tuberculosis. Rich[19] has challenged the dependence of immunity upon allergy in this disease on the basis of a series of experiments in which Rothschild, Friedenwald, and Bernstein[37] desensitized tuberculous animals to tuberculin and found their immunity unimpaired. Other studies by Rich and his associates[38, 19] present evidence that immunity to experimental *Treponema pallidum*, *Pneumococcus* (Type I), and *Pasteurella aviseptica* infections is also independent of allergy. Rich therefore concludes that allergy and immunity are unrelated. Allergic inflammation, however, is the result of antigen-antibody reaction in the tissues. Immunity also depends, in part, upon the action of antibodies upon the invading microorganisms. In short, both phenomena represent *in vivo* tests for the presence of antibody. It is difficult, on theoretical grounds, to believe that they are separable.

It would seem that, in designing an experiment to test the relation of allergy to immunity, the first prerequisite is to determine which antigen of the given microorganism is associated with invasiveness. Antibody to this antigen is the factor which determines immunity. This information is available for only a limited number of microorganisms, notably for such encapsulated organisms as the pneumococci, *H. influenzae*, and the Fried-

länder's bacillus, for the *Str. hemolyticus* group A, and probably for certain enteric organisms.

Little work has been done which is directly designed to correlate immunity with allergy to the specific antigenic fraction of a bacterium responsible for infection. Protection against infection in mice with the Group A hemolytic streptococcus is achieved by the use of antiserum containing antibodies to the type specific M protein. The studies of Bailly[39] concerning hemolytic streptococcus (Type 30) infection in rabbits were designed to examine the question of the relation of allergy to immunity in streptococcus disease. Rabbits which had circulating precipitins and positive tuberculin-like skin reactions to both the type specific M protein and the group specific C carbohydrate were desensitized by the intravenous injection of either the M protein or the C carbohydrate. Precipitins and skin tests to the antigen used for desensitization became negative. Those rabbits desensitized with C carbohydrate, but with circulating antibodies and positive skin tests to M protein, proved to be immune to infection with the type 30 streptococcus Those animals desensitized with M protein, although still having positive skin tests and antibodies to the C substance, lost their immunity to the type 30 streptococcus and died, when they were challenged with this organism. In this case, had only the allergic reaction to the C carbohydrate been considered, immunity would have appeared to exist in the absence of allergy. When the allergy to the vital M protein was studied, however, immunity was lost when allergy was lost.

It is not yet known which of the numerous constituents of the tubercle bacillus is associated with the capacity to infect. The tubercle bacillus possesses at least five proteins, two carbohydrates, and also phospholipids.[40] Tuberculin (PPD) is one of the five proteins. There is reason to believe that tuberculin can be excluded as a factor in virulence, since the capacity to produce tuberculin is not limited to virulent organisms.[41] If, then, tuberculin does not determine invasiveness, antibodies to tuberculin cannot protect, nor can their absence deprive the host of immunity. Hence, allergy to tuberculin is a mark of immunity only in so far as it is correlated with the presence of an immunizing antibody. Desensitization to tuberculin should be expected to leave immunity to infection intact. It is even possible that desensitization with tuberculin might have a beneficial effect on this disease, provided the desensitizing injection was not responsible for focal or constitutional reactions.

In summary, it would seem that the problem of the relation of allergy to immunity is one that can be properly studied only in those infections where the particular antigenic fraction of the organism responsible for virulence is known. Furthermore, the experimental data presented here indicate that more basic knowledge concerning the factors which lead to bacterial invasion and host response must be at hand before many of the problems relating to the allergies of infection are solved. Indeed, only recently tools of sufficient precision have been available. The newer methods of immunochemistry make possible the antigenic analysis of bacteria, the association of one fraction with virulence, the quantitative estimation of antibodies,

and the analysis of types of reaction between antigens and antibodies. As these methods are applied to this field, the problems of the allergies of infection and their relation to immunity will be clarified. At the moment the field is almost entirely unploughed, due, in part, to the diversion of man power to the meadows of antibiotics. Yet it has more than academic interest, for chronic diseases in which allergy may play such a significant role are sometimes those as yet uncontrolled by the chemotherapeutic agents. Furthermore, information gained concerning allergy in infection must add also to the understanding of other allergic diseases. This constitutes one of the real frontiers of medicine and a challenge to the newest methods of immunochemistry.

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IMMUNOLOGIC CHANGES BROUGHT ABOUT BY FUNGI AND FUNGOUS PRODUCTS

By Marion B. Sulzberger

Professor and Chairman of Department of Dermatology and Syphilology, Skin and Cancer Unit and Post Graduate Medical School of New York University—Bellevue Medical Center.

From a very early date, research on the immunologic reactions produced by fungi has served as a sort of pioneer system of experimentation for the investigation of infections in general. Interest in experimentation with fungi lies not solely in the importance of fungous diseases themselves but also, as Bloch pointed out as early as 1908, in the fact that studies of fungous infections are such excellent simple means for investigating the immunologic happenings which occur in infections in general and that, in particular, there is such a close analogy, and in many respects identity, between the results of immunologic studies with fungi and those with the tubercle bacilli.

Paradoxically enough, the recognition of pathogenic fungi can be said to have been the very beginning of the bacteriologic era. Indeed, Schoenlein's recognition of the genus *Achorion* as the cause of favus represents the first sure identification of a microorganism as the causal factor of a human disease. Further, one may fix the beginning of the immunology of fungous diseases as far back as 1902, when Plato and Neisser produced and employed trichophytin extracts analogous to the crude tuberculin of Koch. Very early, Gruby, and much later Sabouraud, two French dermatologists, studied the clinical manifestations of fungous infections of the skin, hair, and nails. They engaged in the clinical description and the cultural and botanical classification of the various types of fungi found in man and concluded that different diseases were caused by different fungi, not by the same fungus. Sabouraud showed that each species of fungus had a tendency to produce a particular form of disease.

After this great advance, however, the subject was dead for many years. It appeared that most of the known fungi pathogenic to mammals had been classified and that nothing very startling or new remained to be described. This stagnation lasted until 1907 or 1908, when Bloch introduced the animal experiments into the studies of fungi. This inaugurated a long series of studies by many men. Then came a great list of workers, topped by J. Jadassohn, one of the originators, including Jessner, Truffi, Martenstein, Biberstein, W. Jadassohn, Saeves, Kogoj, and many others.

Animal experiments with dermatophytic fungi were soon found to have substantial advantages over experiments with many other forms of pathogenic microorganisms. For example, the animals were not killed by the disease, nor was absolutely exact dosage required. The disease was practically confined to the skin and its appendages, so that everything that happened could be observed directly and at desirable intervals, histopathologically, microscopically, immunologically, and in many other ways. Then there were no special precautions to be taken in the laboratory to pre-

vent human infections or cross-infections among the experimental animals. Above all, there was usually a uniform consistency and predictability in the course, development, and regression of the disease. To my knowledge, there is no other experimental disease where there is such fine regularity and so little variation in time intervals as there is in the skin and hair infections of the guinea pig with *Achorion quickeanum*.

Experimental Results and Inferences After Infections and Reinfections

With such experimental fungous infections and reinfections of the skin of laboratory animals with *Achorion quickeanum*, many fundamental immunobiologic principles of infection have been demonstrated with the utmost clarity and at a very early date. Many of the immunobiologic findings preceded those in tuberculous and other infections. Indeed, many immunologically significant facts have been demonstrated exclusively in experimental fungous diseases. Thus, the wealth of immunologic lore is far greater in relation to fungous infections than to any other infectious diseases affecting man. The following are selections from among the most important findings.

First Infection. On first infection there is a regular incubation period which lasts about 10–14 days. At the end of this period, the phenomena noted include the following: (*1*) clinical and histopathologic inflammatory changes appear at the inoculation site; (*2*) as a rule, the trichophytin skin test (intradermal injection and 24–48 hour reading) becomes positive, roughly coincidentally with the first appearance of clinical manifestations; (*3*) as a rule, the more inflammatory the lesions, the greater the trichophytin sensitivity of the skin; (4) as a rule, the more inflammatory the lesions, the greater the tendency to local healing and the less easy it is to demonstrate fungi by direct microscopic or by culture methods.

When one performs trichophytin skin tests at various intervals after healing of the local lesions, one finds that the trichophytin hypersensitivity acquired as the result of the infection is usually long-lasting, often persisting for the lifetime of the animal.

Reinfection. If one takes a guinea pig which has recovered from a previous infection and reinfects the animal at another skin site with the same fungus, one finds that there is occasionally, perhaps rarely, a complete immunity and failure to produce disease. Usually, however, an infection of modified form and course takes place at the reinfection site, the lesion appearing within a few hours, instead of after an incubation period of many days. Moreover, the healing sets in much earlier after reinfection than after the first infection. The recovery is generally complete in from 10 to 12 days, instead of about 21 to 28 days. The obvious reason for this accelerated course is that the incubation period (*i.e.*, the period needed for the development of immunologic changes which lead to trichophytin hypersensitivity) is no longer required in the *reinoculated* animal, which has retained a persistent trichophytin hypersensitivity as a result of its previous infection.

Inferences. It is from findings of this kind that the following inferences may be drawn:

(*1*) The development of hypersensitivity to the fungous allergens contained in "trichophytin" is intimately connected with the appearance of the inflammatory disease.

(*2*) The degree of trichophytin hypersensitivity of the tissues is intimately connected with the severity of the manifestations, the time intervals required for the disease to appear and to run its course, the tendency to healing, and the number of fungi present and demonstrable in the lesions.

In translating these inferences to human disease or to infections in general, one may arrive at the following postulates:

(*1*) The diseases produced by these groups of fungi (hyphomycetes-dermatomycetes) are probably *not* caused by toxins or poisons elaborated by the microorganisms, but are most likely caused by fungous *allergens*. The diseases are thus, from their inception, immunologic or allergic sensitizations, in this respect, just like anaphylaxis or hay fever or contact-type eczematous dermatitis from plants, dyes, or other simple chemicals. Moreover, as shown by Bloch, Schaaf, and Labouchère in 1924, one of the most important allergenic principles in these fungi is a polysaccharide and no at protein.

(*2*) The fungous diseases of this type are, thus, analogous to numerous important diseases, such as tuberculosis, leprosy, and syphilis, in that, in these latter also, the microorganisms are not known to produce any toxins or intrinsically damaging substances, but do produce allergens or immunologically active substances which sensitize the tissues and which then give rise to the local allergic reactions which constitute the principal manifestations of the disease.

(*3*) On the basis of these principles, presumably, one can divide microorganisms and the diseases they produce into several categories:

(*a*) Allergenic microorganisms and the principally allergic diseases, such as fungous infections, tuberculosis, leprosy, syphilis, and many others.

(*b*) Toxin- or poison-producing microorganisms and the diseases they produce, such as diphtheria, tetanus, *etc.*

(*c*) Microorganisms which have combinations of allergenic and toxic action, *e.g.*, streptococci in scarlet fever, certain staphylococci, *etc.*

(*d*) Microorganisms producing disease by still other mechanisms (*e.g.*, competition for and withdrawal by the microorganism of substances vitally needed by the tissues of the host; synergistic or summation effects of microorganisms plus other agents; and mechanical or chemical destruction, or obstruction, embolization, coagulation, lysis, *etc.*).

While I should like to enlarge upon the many clinical and theoretical significances of the facts and inferences just sketched, I shall have to confine myself to just a few points of practical importance.

In contrast to what is done in achieving antitoxic immunity in the toxin-forming infections, if the ideas expressed are correct, the allergic infectious diseases should, in theory, best be prevented and treated by desensitization or hyposensitization measures, in analogy to the manner in which anti-anaphylaxis is produced in animals or hay-fever patients are desensitized or hyposensitized with the specific pollen allergens. Indeed, as Wise and

Sulzberger showed in 1932, in many cases of fungous diseases, the skin's sensitivity to trichophytin can be substantially, if only temporarily, reduced by repeated intracutaneous injections of trichophytin. Also, in some such cases, there was a concomitant improvement of the fungous disease. However, we stated that the method, at present, was of negligible therapeutic or practical value because of the many unpredictabilities. Included among these was the uncertainty as to which patients, instead of a lowering, would develop a great increase in trichophytin sensitivity and a concomitant worsening and/or spread of their allergic fungous disease. Moreover, even when the level of the skin's sensitivity to trichophytin could be reduced by the repeated injections, this reduction was usually transitory, there being a strong tendency for each skin to return to its previous "natural" level of sensitivity. Here again, the many resemblances to the results of tuberculin desensitization in the treatment of tuberculosis will be obvious.

Even a cursory contemplation of the findings and their implications should show that it is fruitless to argue about whether the hypersensitivity to allergens of microorganisms (trichophytin or tuberculin hypersensitivity, *etc.*) is protective or harmful. If the author is correct, then the hypersensitivity is, first of all, the *sine qua non* of the disease and thus, in that sense, unequivocally and obviously harmful. However, connected with, and perhaps resulting from, this very hypersensitivity and the resulting tissue reactions, many forms of beneficial and protective tissue reactions can occur, for example: the more rapid local destruction and throwing-off of the microorganisms; the inflammatory demarcation of the affected sites; the retardation or prevention of dissemination and spread of microorganisms and their products; and the inflammatory mobilization and *taxis* to the affected site of many other means of protection (*e.g.*, hyperemia, lysins, agglutinins and other protective antibodies, leucocytes and lymphocytes, *etc.*).

Thus, the hypersensitivity is: (*1*) very harmful locally; and (*2*) may be one of the great beneficial and protective factors to the host as a whole. It is, however, in most instances, neither one nor the other exclusively.

The findings, that the higher the degree of trichophytin sensitivity which a fungus produces, the greater the local inflammation, the more difficult it is to demonstrate the microorganisms in the tissues, and the greater the tendency to rapid course and spontaneous healing, all help to explain why certain fungi are more inclined than others to cause little or only superficial inflammation but are highly contagious from man to man, producing seemingly mild diseases which are, paradoxically, often the most difficult to cure.

The fungi of this group I have termed "anthropophilic", because of their predilection for man, contrasting them with the "zoophilic" fungi, *i.e.*, those which prefer to infect lower animals, but which, when they do cause sporadic cases in man, produce greater trichophytin hypersensitivity, greater and deeper inflammation, and a more distinct tendency to spontaneous cure.

These observations and classifications are of practical significance just

now in regard to the difficulties of controlling the present epidemic of scalp infections of children with the anthropophilic, poorly sensitizing *Microsporon audouini*, in contrast to the sporadic cases of more inflammatory, more readily curable scalp infections with the more highly allergenic *Microsporon lanosum* or *Microsporon canis*.

It is, moreover, noteworthy that *Trichophyton purpureum*, another fungus with a low potential for producing sensitizations with 24–48 hour inflammatory-type reactions to trichophytin (but which, as shown by George M. Lewis and co-workers, produces mainly immediate, wheal-type sensitizations), is also the cause of some of the most stubborn and therapy-resistant forms of superficial fungous disease of the skin.

I should like, at this point, to go into the many other immunologic facts and findings in which experiments with fungi and fungous allergens have done the pathfinding. For example, I should like to present, with the detail they merit, the studies of J. Jadassohn and his school on the immunologic basis of local and hematogenous first infections, reinfections and superinfections; those of M. Jessner on the very early immunity in experimental sporotrichosis; and those of Stephan Epstein and collaborators, who showed that a zone of local specific immunity forms at the center of the "ringworm" patch on human skin and that such an immune zone also forms at and beyond the border of the enlarging patch. Thus, in Epstein's classic studies, specific but local immunologic changes were proven to occur and were shown to account for the configuration of certain characteristic skin lesions, as well as for the noteworthy and fortunate circumstance that a local infection usually does not spread to cover the entire body surface but stops enlarging when it reaches a certain extent, mainly because it builds up a circumferential immunity which blocks its own further extension. I should have liked also to discuss the pathogenesis and immunology of the secondary eruptions known as trichophytids, as demonstrated by J. Jadassohn, Bloch, W. Jadassohn, and co-workers. Most particularly, I regret that space does not permit me to give proper exposition to the basic and significant findings of W. Jadassohn and his collaborators on the relationships of fungous hypersensitivity to anaphylaxis and on the use of the Schultz-Dale experiment and the Prausnitz-Kuestner experiment for the demonstration of the characteristic but complex and composite mosaic of the allergenic principles developed by each different species, strain, and family of fungi.

Due to lack of space, however, I must refer the reader to the very adequate literature on these subjects, appended herewith in the bibliographic list.

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FAMILIAL NONREAGINIC FOOD ALLERGY

By Milo G. Meyer
Gardner Medical Group, Michigan City, Indiana

Familial nonreaginic food allergy, or "idioblapsis," owes its name to Dr. Arthur F. Coca. It is a highly controversial subject. If the assumptions which, for the most part, Dr. Coca and I believe to be true become established facts, the mystery as to the etiological factors of previously unexplained illnesses will be removed. If, however, we should be found mistaken, those of us who are successfully using the knowledge of this allergy as a therapeutic aid are running the risk of professional condemnation and ridicule. Further, we could only attribute the results obtained to the effect of psychological suggestion on unstable and neurotic patients. This paper, then, is written not in defense of the existence of such an allergy but, rather, out of my own experience, in an attempt to explain further the rationale of the conclusion that there is an extraneous factor which not only precipitates a disordered mechanism of bodily function but, also, renders the organism susceptible to the ravages of certain infectious agents.

Of necessity, constant reference must be made to Dr. Coca's[1] book on this subject. Having had the opportunity of testing his radical ideas in a certain group of patients typical of those seen by the average internist, I belive very serious consideration of his theories is warranted. Thus, this paper will be divided into the following sections: (1) theory; (2) practical application; (3) results obtained. From this division, it is hoped to prove the existence of idioblapsis as an entity.

Theory

"Idioblapsis" is derived from blapsis, a "spoiler," and idio, which conveys the meaning of individual peculiarity. Familial nonreaginic food allergy, as pointed out by Coca, adequately expresses the thought, were it not for the fact that other excitants besides foods also conform to the fundamental requirements of its definition. TABLE 1 illustrates the important aspects in which this group of allergies differs from atopy, allergy of infection, serum disease, and contact dermatitis.

We contend that the symptoms and illnesses shown in TABLE 2 are generally derived from food allergy. It is obvious to all that there are the complaints which comprise the vast majority of illnesses seen in the average physician's office and for which, to date, only symptomatic therapy is being given. Some of these have, in Dr. Coca's experience and in my own, responded so brilliantly to exclusion therapy that we believe there is little doubt as to allergic etiology.

This phase of allergy is not well worked out. Most allergists depend on the cutaneous reaction as a means of solving the individual's problems. The other method is to subject the patient to the unwieldy and discomforting process of a long series of elimination diets. The latter falls short of the expected goal because food sensitivity is a very individual problem,

and, as we shall show later, diets do not take into consideration that any one food whatsoever may be the causative agent in the patient's illness. The cutaneous test, according to figures which Dr. Coca and I have checked, fail in their diagnostic ability in this phase of allergy more than 75 per cent. This will be shown in a later table.

The incidence of atopy among the food-allergic patients studied by Coca seems to be fixed at about 5.7 per cent in young people. This is shown in

TABLE 1

CHARACTERISTICS OF IDIOBLAPSIS

1. The hereditary influence controlling its occurrence is independent of the atopic inheritance.
2. Allergic antibodies (reagins) are not demonstrable.
3. Many of the symptoms are not represented in the atopic group.
4. The allergic reaction practically always causes acceleration of the pulse.

TABLE 2

SYMPTOMS PROVISIONALLY RECOGNIZED AS FOOD-ALLERGIC IN 54 PATIENTS. ALL SYMPTOMS WERE ACCOMPANIED BY TACHYCARDIA AND ALL DISAPPEARED AFTER ELIMINATION OF THE FOODS THAT CAUSED TACHYCARDIA

Symptoms	*Number of patients affected*	*Symptoms*	*Number of patients affected*
Headache, migraine (7) Headache, severe (11) Headache, mod. (20)	38	Irritability	3
Physical tiredness	36	Chest pain	3
Nervousness	23	Abdominal pain	3
Indigestion, including gas, vomiting, nausea	21	Angioneurotic edema	3
Dizziness	20	Gastrointestinal bleeding	2
Constipation	16	Pain in gall-bladder	2
Neuralgia	15	Conjunctivitis	2
Canker sores	13	Gastric pain	2
Chronic rhinitis	13	Angina pectoris	2
Heartburn	11	Diarrhea	2
Urticaria	9	Colitis	1
Epileptiform seizures	7	Anorexia*	1
Overweight	6	Chronic cough	1
Psychic depression	3	Dysmenorrhea	1
Extra systoles	6	Frequent epistaxis	1
		Nervous and emotional instability	1
		Chronic bronchitis	1

* Possibly due to deficiency of vitamin B.

TABLE 3. Independently of this, I have a small series of sixty cases in which atopy appears in about 18 per cent. This is shown in TABLE 4.

The rather high incidence, I believe, may have been due to extremely careful questioning, which may have made the patient desirous of attempting to support positive answers to my questions. These figures are obtained by history, not by skin testing. It would seem, then, if one is correct in the assumption that we can explain the patient's symptoms on the basis of allergy, to date at least, that the sensitization of the cardiovascular appara-

tus is the only accurate way of arriving at a satisfactory opinion as to the allergens involved. TABLE 5, taken from Coca, indicates the results of cutaneous tests. (Note that only in MMD, CB, and JJV, *all asthmatics*, positive tests appear; in the remainder, direct intra-cutaneous tests and tests in substitute are negative. This percentage is much smaller than the 30 per cent which I originally indicated.) In an attempt to confirm this in a small way, ten patients of my own are shown, in whom the pulse dietary tests as well as intracutaneous and scratch tests were used (TABLE 6).

Although several other observers[2] have recognized the existence of a curative effect by the elimination of certain foods, the percentage of success, when a diagnostic dependence is placed on cutaneous tests, will of necessity

TABLE 3

SHOWING THE OCCURRENCE OF ATOPY AMONG 191 FOOD-ALLERGIC PERSONS AND 69 PERSONS FREE OF FOOD ALLERGY

Familial nonreaginic food allergy	191	(74.5%)	Atopy	11	(5.7%)
No food-allergy	69	(25.5%)	Atopy	4	(5.7%)
Total	260	(100.00%)	Atopy	15	(5.7%)*

Patients who have been under the dietary treatment for nonreaginic food allergy are not included in this survey. The individuals making up the group were taken at random among residents in a suburban town (Oradell, New Jersey) and among nurses in the nearby Hackensack hospital.

* No doubt the smallness of this percentile incidence of atopy is due to the fact that the group is composed largely of children and young adults.

TABLE 4

THE OCCURRENCE OF ATOPY AMONG 50 FOOD-ALLERGIC PERSONS AND 10 PERSONS FREE OF FOOD ALLERGY, ALL OVER AGE 30

Familial Nonreaginic Food Allergy	50	Atopy	9	(18%)
No Food Allergy	10	Atopy	1	(10%)

be small. Since the pulse response is the diagnostic criterion concerned, we must consider its mechanism. This is now only speculative. It is apparently well agreed that there is an independence of the shock organs or areas; that is, that each organ or system retains an independence of reaction to the insulting substance. This would strongly suggest that the reacting substance is cell-bound or sessile, but does not explain why, when excitants are avoided for a comparatively long time, the reaction to their next insult is lacking. The acceleration of the pulse, according to Coca, is specific in every case. He feels this so strongly that he makes no exception. The specificity is apparently almost 100 per cent. I am sure, however, that I have seen two patients who have proven food allergy and yet I have failed to demonstrate an increased post-prandial heart rate. FIGURES 1 and 2 indicate this observation. These are the *only* two cases so far encountered and they are not sufficient to disprove Coca's theory, since both cases were responsible for their own pulse rates.

In an attempt to build a platform on which to explain the sensitization of the cardiovascular system, one may turn to the histamine theory. We

then assume that the shock tissue, when insulted, liberates a histamine-like substance which increases the heart rate, either because of blood vessel caliber alteration following the sympathetic nervous system stimulation

TABLE 5

RESULTS OF CUTANEOUS TESTS IN 32 SUBJECTS OF FAMILIAL NONREAGINIC FOOD ALLERGY FIGURES INDICATE THE NUMBER OF DIFFERENT FOODS USED IN THE TESTS; ALL OF THOSE FOODS HAD CAUSED TACHYCARDIA IN THE RESPECTIVE PERSON

Patient	*Direct intracutaneous tests*	*Indirect tests in a substitute*
E. F. C.		Negative (3)
A. F. C.		Negative (8)
M. M. D. (asthma and hay-fever)	Negative (4) Positive (1)	
C. T.	Negative (5)	Negative (4)
J. G.	Negative (2)	
A. R.	Negative (1)	
L. R.	Negative (3)	
S. H.		Negative (3)
W. W. F.		Negative (2)
M. F.		Negative (3)
M. A.		Negative (6)
P. W.		Negative (4)
E. B.	Negative (2)	
C. B. (asthma)	Negative (2) Positive (2)	
R. M.	Negative (5)	
J. J. V. (asthma)	Negative (9) Positive (3)	
J. K.	Negative (11)	
J. F.	Negative (8)	
W. S. C.	Negative (3)	
J. V.	Negative (13)	
M. N.	Negative (4)	
R. F.	Negative (7)	
N. vW.	Negative (9)	
L. H. B.	Negative (21)	
Mrs. E. B.	Negative (6)	
A. S.	Negative (15)	
M. S.	Negative (6)	
W. G.	Negative (2) Neg.-sl. (1) not passively Slight (1) transferable	
M. P. age 11 (grandmother, G. B. asthmatic)	Negative (6) Positive (1 and dust)	
G. B. (asthma)	Negative (3)	
E. K.	Negative (2)	
G. H.	Negative (16)	

In some patients tests were not made with some of the known allergenic foods. Negative tests with nonallergenic foods are not included.

or by a direct effect on the cardiac accelerator or inhibitory center. This may also explain the loss of pulse acceleration after repeated ingestion of the offending food. Several investigators[3] have shown that the response to histamine itself is quantitatively lessened after either repeated injections at the same local site or by the injection of one large dose in saline. This in-

TABLE 6

COMPARISON OF PULSE-CRITERION AND SKIN TEST IN TEN ALLERGIC PATIENTS

Patient	*Age*	*Symptom complex*	*Allergens causing tachycardia*	*Allergens by skin tests*
H. B.....	62	Rhinitis	Potatoes, beef, corn	Pollens, only has seasonal hay-fever
L. N.....	38	Migraine	Tomato, egg, oat, coffee	None (histamine 4 plus)
B. G.*.....	16	Acne	None	Chocolate, egg
V. H.....	34	Asthma Diarrhea	Beef, egg, orange and wheat	Egg, corn, rye, milk, dust pollens
R. J.....	24	Pruritus	Egg	None
A. K.....	52	Hypertension	Egg, coffee, banana, cereals	None
M. M.....	50	Hypertension	Potato	None
C. L.....	38	Hypertension	Dairy Products, nuts	None
F. M.....	62	Hypertension Pruritus generalized Arthritis	Pork, corn	Veg. oil, feathers, dander, dust, wool
M. R.....	28	Menière's syndrome	Pears, peaches, apples	None

Note that a case of acne failed to show pulse acceleration, although skin tests to chocolate and egg were positive. The acne has *not* cleared with the elimination of chocolate and egg. In one asthmatic, tachycardia and whealing to egg are shown. In no other case is there similarity.

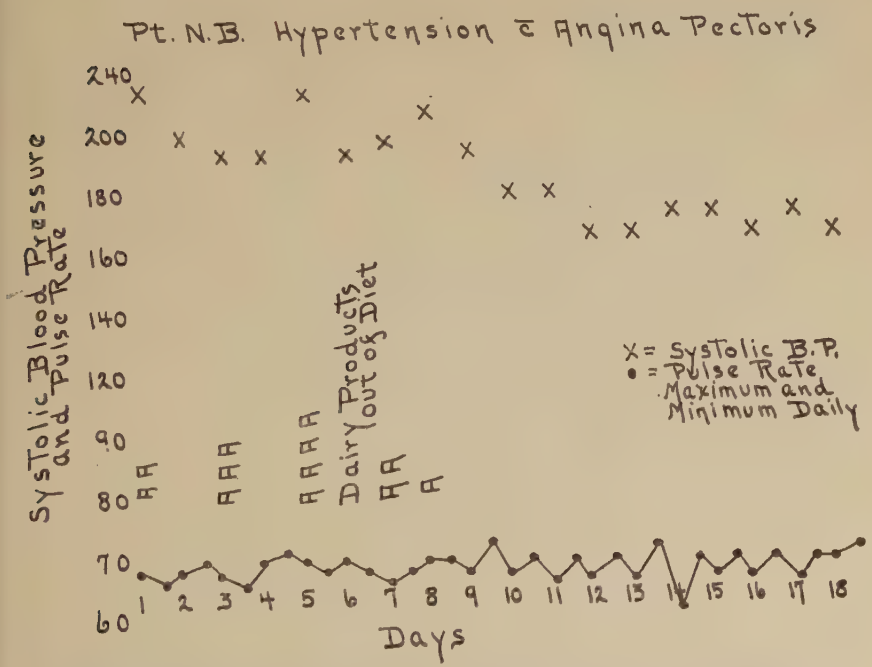


FIGURE 1. The hypertension in NB is apparently relieved with elimination of dairy products; yet, according to the pulse chart which she kept, there is no variability in rate before and after elimination.

creased tolerance persists for as long as twelve hours, probably much longer. This reaction must be nonspecific as far as the sensitizing agent which liberates a histamine-like substance is concerned. That fact was established by Farmer[4] in 1922. I have attempted a correlation of pulse rate before and after histamine injections with certain allergens remaining in the diet. The result in three of my patients is shown in FIGURE 3.

The exact mechanism involved is, therefore, not completely rationalized and the premises given are only suggested. That the autonomic nervous system is involved in this increased pulse rate is very strongly suggested by the stability of the pulse rate after the severance of the sympathetic chain

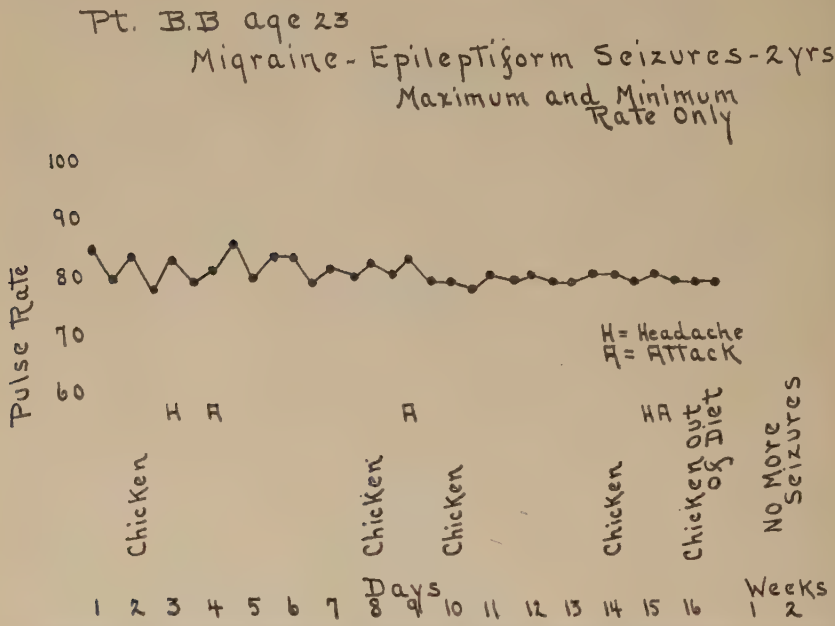


FIGURE 2. The epileptiform seizures and headache in BB were lessened, with no seizures for several weeks while eliminating the foods and with very little change in pulse rate before and after.

However, the acceleration is not completely eradicated when selected food allergens are still ingested. It is worth pointing out also that anti-histamine agents do not cure these people, which is a strong argument against histamine's being the sole factor.

The practical application of this interesting study is beset with many baffling problems. It is naturally dependent on an intact cardiovascular apparatus which is not being influenced by extremes of emotional excitement, physical exertion, febrile illness, or marked metabolic derangements.

The normal pulse is remarkably constant when not insulted by allergens. This is shown in FIGURES 4 and 5—the first from Coca's book and the next on two hard-working individuals, one age 28 and the other age 61, and on two people of my own acquaintance who have no complaints and no personal or family history of familial allergy. It is also shown on these tables that

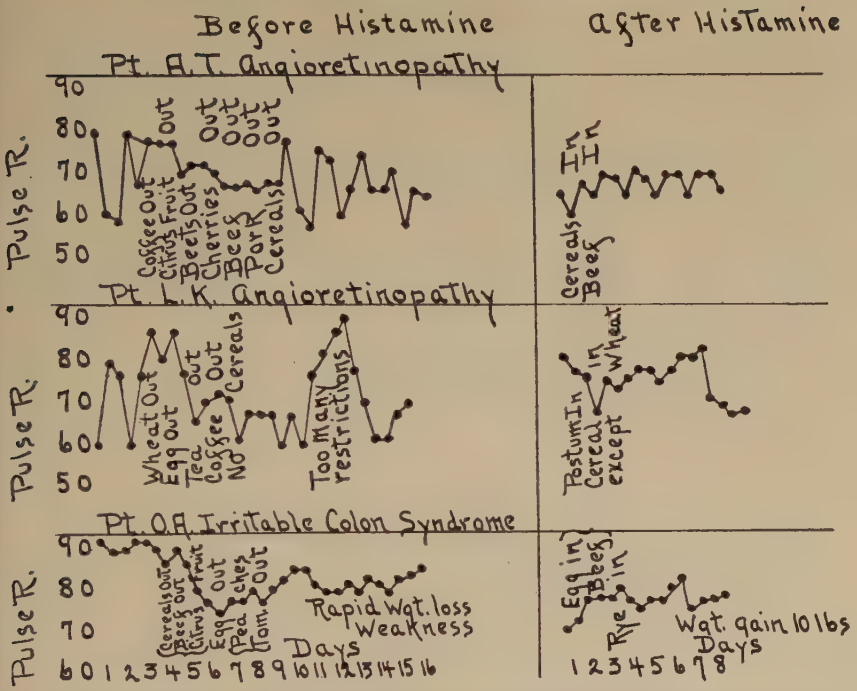


FIGURE 3. In patient AT, the pulse still remains stable when cereals and beef are reintroduced while histamine Azoprotein is being given. In LK, cereals except wheat were reintroduced without pulse acceleration. In OA, egg and beef were reintroduced with a stable pulse still manifest when the histamine tolerance is built up.

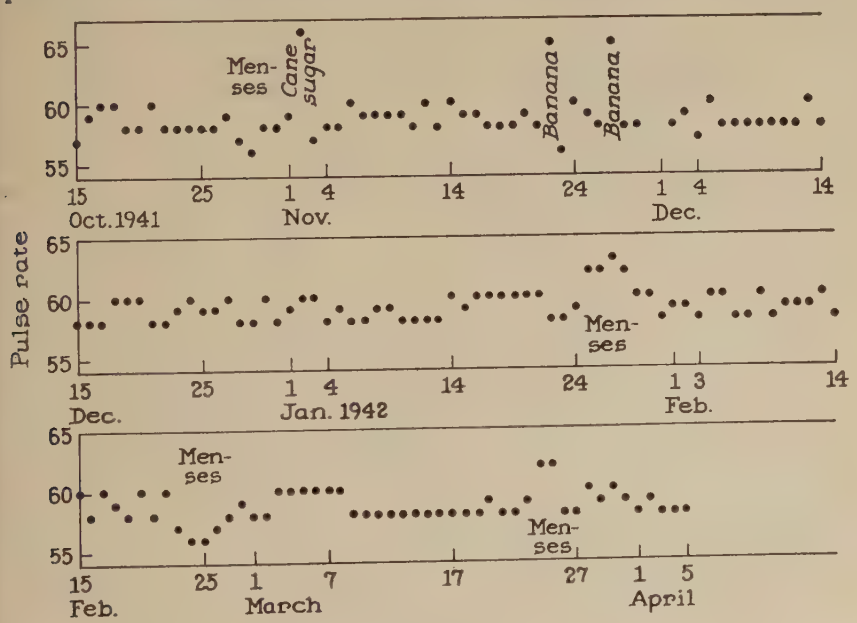


FIGURE 4.

the pulse is not stable when specific irritants are ingested. No restriction of activity was imposed on the people whose records are graphically illustrated.

This method may also be used in diseased hearts. I mention this only to show that, with the conduction apparatus severed, a response still occurs. This is illustrated by the influence on the apex rate of auricular fibrillation in two individuals whose fibrillation was on the basis indicated in FIGURE 6.

There is then a definite stability of the pulse rate in food allergic persons when the irritants are avoided. This was demonstrated by Coca on sixty-

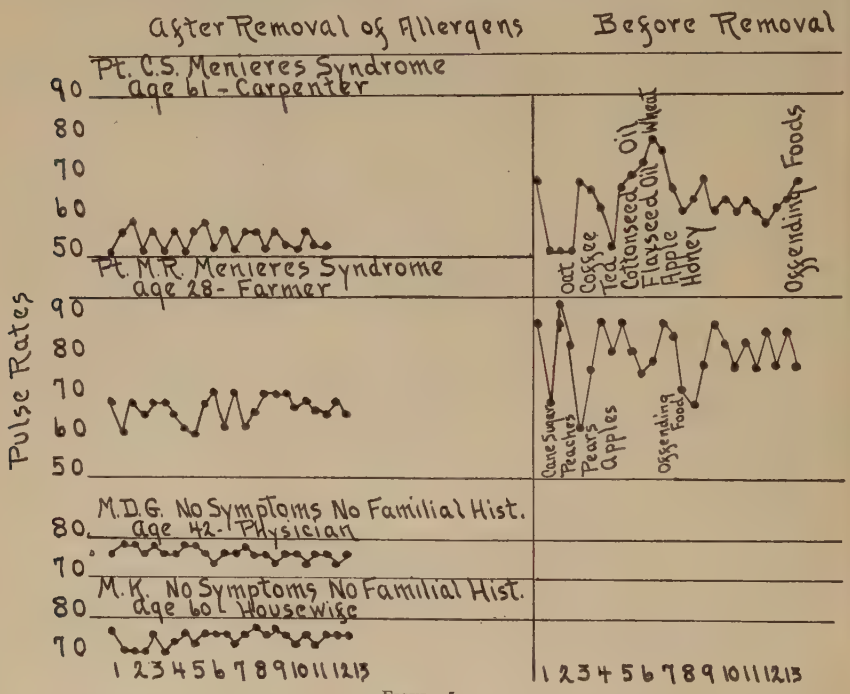


FIGURE 5.

two cases in whom he had successfully removed the allergenic foods. I should like to corroborate this with one hundred and six cases of my own who now not only have pulse stability but also have good health. These studies have naturally excited curiosity on the part of our own medical group. For a period of time, all patients, regardless of complaints, except pregnancies and traumatic cases, had pulse checks in our clinic, and thirty of those who were apparently the most co-operative recorded their heart rate after each meal, with the results shown in TABLE 7. The 60 per cent incidence leaves a relatively small number with stable pulse. Even in those, the stability may be on an accelerated plane due to the fact that the average pulse rate is *much lower* than we formerly thought.

Practical Application

It is imperative that the problems which will be encountered by the physician attempting this study be thoroughly understood. The failure to gain results and discouragement on patient's and physician's part can be

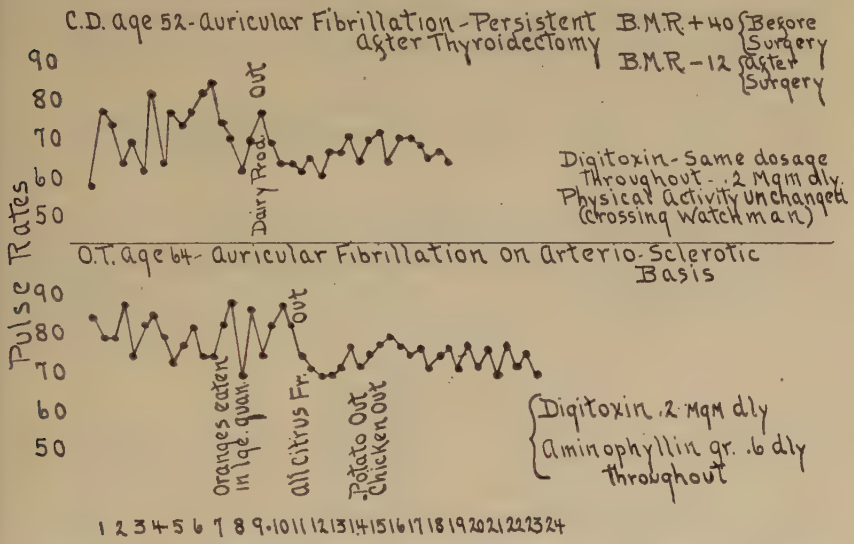


FIGURE 6. Note that medication was unchanged throughout the study. Physical activity was also unchanged before and after the removal of allergens. Fibrillation, however, is still persistent.

TABLE 7

No. of patients	Pulse over 80 in 2 readings
200	143 (71.5%)

No. of patients	No. with pulse variability p.c. of over 12	No. with personal and familial history suggesting idioblapsis
30	18 (60%)	16 (53.3%)

This indicates food allergy in about seventy per cent of the two hundred, except that diseased hearts were included. Of the thirty taken at random, regardless of complaints, but without known heart diseases or fever, food allergy is suggested in 60 per cent and is corroborated by history in 53.3 per cent.

avoided to a large extent by, first, a careful evaluation of the patient and, second, a very careful understanding of the method of interpretation.

The initial questions to be considered with the presenting patient are primarily three in number. These are indicted in TABLE 8. The first of these is best answered by having the patient, following his first office visit, carefully fill out the questionnaire reproduced in TABLE 9. This can be followed up and in most cases can be combined with a diagnostic résumé by giving him a trial diet (TABLE 10). This is a heterogeneous grouping of

common foods used only in the hope of demonstrating instability in the pulse rate with their ingestion. Explicit instructions are indicated not only for the recording of the pulse rates but also to gain complete patient co-operation. The necessity for the original use of enamelware or glassware rather than aluminum is indicated by FIGURE 7 (taken from Coca). This method can, in a large measure, determine the advisability of continuing further investigation. It especially does away with the need of spending much time in oral questioning and conference.

If the decision is such that further investigation is indicated, recourse may be had to one of two methods: (1) the patient may have a "free" diet,

TABLE 8

1. Is the patient a person of food-allergic constitution?
2. Can the chief symptom or symptoms complained of be identified as food-allergic, or is the patient predisposed to them by the handicap of food-allergic pathology?
3. What are the specific excitants of the food-allergic symptoms in the particular case?

TABLE 9

QUESTIONNAIRE

NAME..... AGE.....
ADDRESS.....

If you have had or are having the following, *place a check* (√) *mark after the disorder indicated.*

If any member of your family (mother, father, uncle, children, grandparents) have had or are having these disorders *place an X after it.*

1. Asthma
2. Hayfever
3. Hives
4. Migraine (sick headache)
5. Chronic indigestion
6. Colitis or Diarrhea (chronic)
7. Nervousness
8. Insanity or nervous breakdown
9. Chronic eczema
10. Epilepsy
11. Deafness or severe dizziness
12. Stammering or stuttering
13. High blood pressure
14. Diabetes
15. Canker sores
16. "Shingles"
17. Gall bladder diseases
18. Cancer
19. Ulcers

At what age and under what circumstances did your present disorder start:

with only the limitation of four or five foods at a feeding (this allows them a more pleasant method of determining their allergen); or (2) the patient may be given only one food at a meal (although of some discomfort to the hard-working patient, this presents an easier method of interpretation). The latter method is used by Coca. This admonition should be injected here: If the patient's symptoms are severe enough to cause him to co-operate, few problems are encountered. If they are not, it is useless to attempt to force the issue, because one is certain to meet with disappointment.

Can the chief symptom be identified as being due to food allergy? The

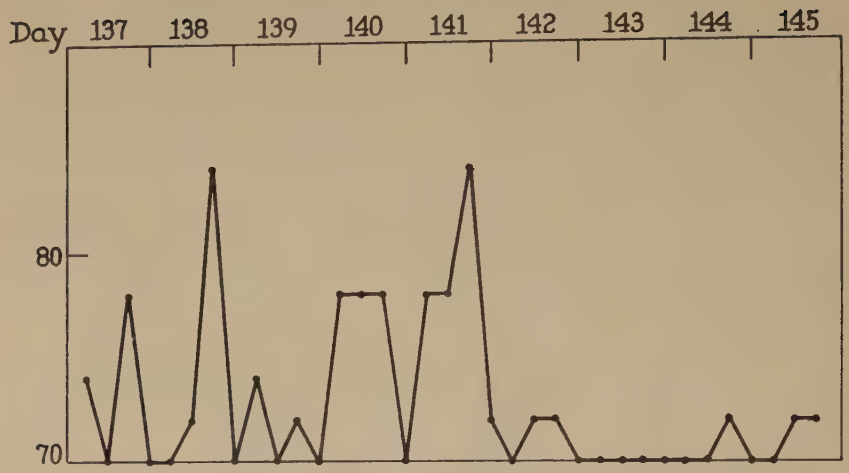
answer to this has, for practical purposes, already been gained by the foregoing questionnaire. The proof, of course, is in the disappearance of the symptoms when the offending substance is removed and, finally, to be therapeutically and scientifically correct, in the return of symptoms when the food is re-ingested. Complete confidence in the doctor is required to convince the new patient that the avoidance of certain foods will prevent the

TABLE 10
PRELIMINARY TRIAL DIET

Pulse rate 4:00 P.M. Day before test starts	8:00 P.M.	9:00 P.M. Before arising 9:00 P.M. Day of test
Menu	*Pulse rates*	*Symptoms*
Rice Milk Beet sugar Grapefruit	Before ½ hr. after 1 hr. after 1½ hr. after	
Beef Peas Potatoes Lettuce (no dressing) Pears (water packed)	Before ½ hr. after 1 hr. after 1½ hr. after	
Rice Beet sugar Milk Butter Cheese Rye-Krisp	Before ½ hr. after 1 hr. after 1½ hr. after	
Second day		*Pulse before arising*
Whole wheat bread Milk Butter Egg	Before ½ hr. after 1 hr. after 1½ hr. after	
Beef Carrots Lettuce Beets	Before ½ hr. after 1 hr. after 1½ hr. after	
Whole wheat bread Peas Chicken Grapefruit	Before ½ hr. after 1 hr. after 1½ hr. after	

development of other disabilities later in life. This, then, can only be done if one can prove that the present difficulties can be eliminated.

The specific excitants of the symptoms are primarily those that cause an increased heart rate. Yet, the disappearance of symptoms may occur with the elimination of only one or two of the foods that cause a heart-rate increase. This is illustrated in FIGURE 8. Note in the discussion that this patient experienced complete disappearance of arthralgia, which was

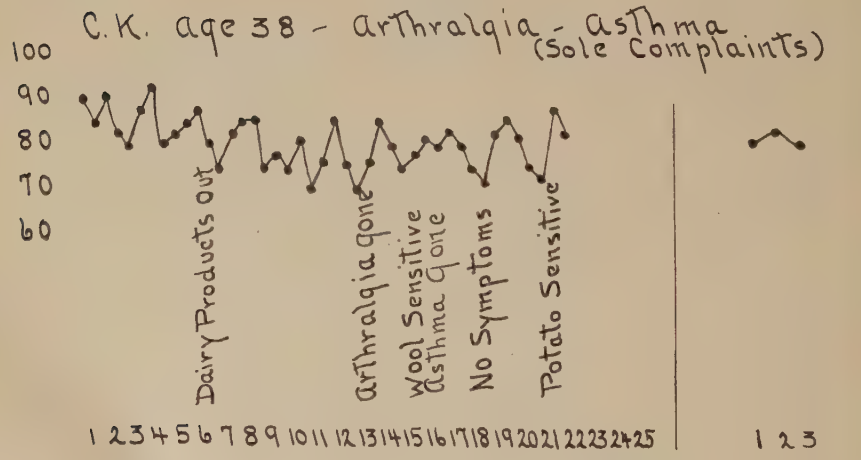


Every day – potato, lettuce, French dressing nucoa, tea and beet-sugar; alternately beef, lamb, fish, fowl, pork.

Cooking in aluminum and other metal

Cooking in enamel-ware

FIGURE 7.



Pt not interested after 3 weeks in eliminating potatoes since she had no subjective symptoms whatsoever from eating them

FIGURE 8J

associated with a tachycardia due to dairy products; yet the pulse is still unstable and the second food is ingested without complaints. Will symptoms appear in later life, as premature aging of certain organs and systems

TABLE 11
FACTORS OTHER THAN FOOD-ALLERGENS THAT MAY CAUSE TACHYCARDIA

1. Smoking
2. Cathartics
3. Emotional disturbances
4. B-complex deficiency
5. Medications having specific effect on C.V. mechanism.
6. Metal cooking utensils
7. Dust
8. Inhalants (tooth powder, illuminating gas, coal smoke, *etc.*)

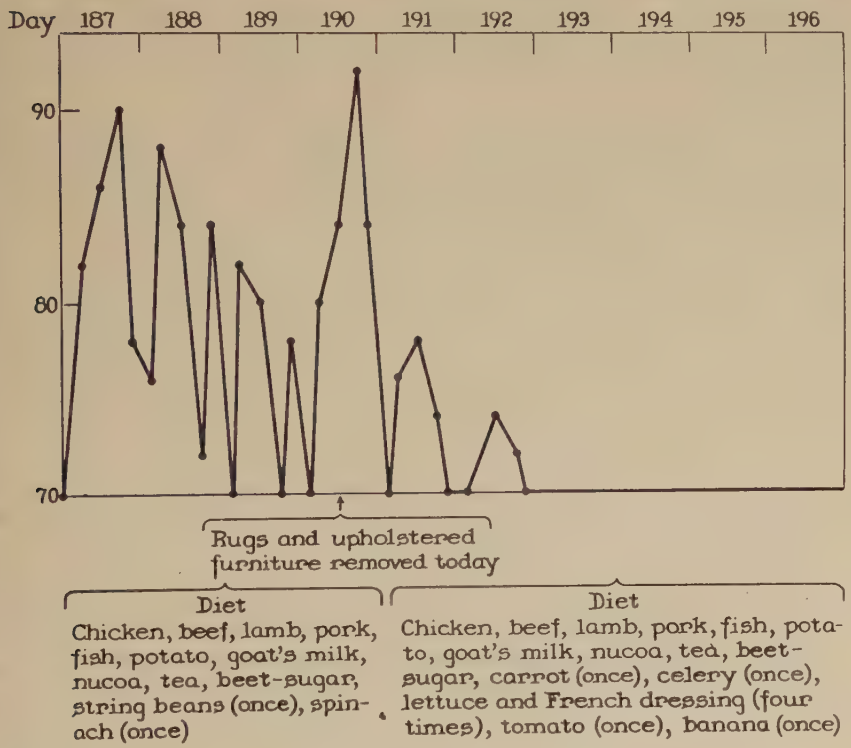


FIGURE 9.

ensue? This question makes us carefully consider major and minor allergens. A discussion of these in detail will be given later.

As mentioned before, it has been shown that other factors than food are involved in a pulse response. These factors must be avoided at the time the diets are being followed. Most of them are listed in TABLE 11. The influence of dust is graphically illustrated in FIGURE 9 (from Coca).

I should like now to discuss in detail the individual difficulties encountered in interpretation and correlation of pulse-rate response. As I stated in the original review of Coca's book, these chapters invite the greatest controversial reaction. The discouragement attendant in those people exhibiting these problems has certainly forced abandonment of solution on many of my own patients. This in spite of personal enthusiasm for the theory. I can understand, however, why many physicians may remain cool to it, after perusing this chapter, with its numerous paragraphs as to why failure of identification may occur.

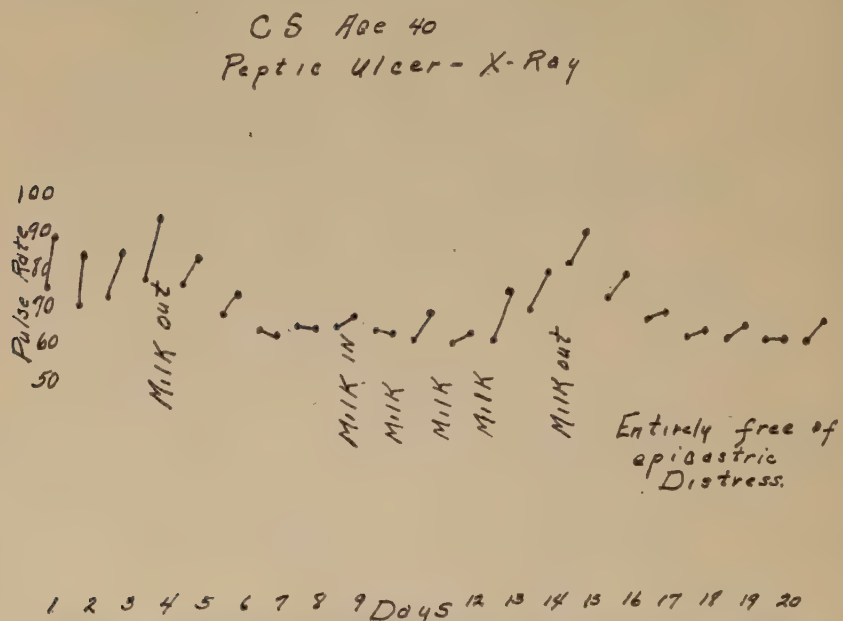


FIGURE 10. Note following primary elimination of milk that, beginning four days later, it was taken fou successive days before any definite acceleration occurred, also that, in both instances, the tachycardia per sisted for forty-eight hours after its elimination.

A concrete physiological explanation and scientific background for the specificity of the pulse-accelerating mechanism has many pitfalls, and its explanations are still debatable. The practical difficulties are also real. The careful study and application of reason as presented will enable those interested to solve most of the difficult cases. The problems are as follows:

(1) *The Latent Period of Temporary Lost Sensitivity.* This is best illustrated in FIGURE 10, graphically representing the temporarily lost sensitivity to milk. This phenomenon of course, is not new, having been mentioned many times by Vaughan.[5] This is another important differentiation from atopy, since loss of sensitivity here is probably due to natural desensitization rather than avoidance.

(2) *The Carry-Over Reaction or Recurrent Reaction.* This is common. I have encountered numerous examples of it as evidenced by the continued

elevation of pulse rate *prior* to succeeding meals when the breakfast has produced tachycardia.

These reactions are not too difficult to interpret. The removal of what are seemingly allergenic foods, however, may result in the elimination of some that are not. In that event, comfort may be impossible and the patient may prefer the chain of symptoms rather than a semi-starvation diet. I have found that a careful review of these cases in intervals of leisure is the only way to avoid the incrimination of food that is not allergenic.

(3) *Major and Minor Allergens.* This is one of the really discouraging phenomena of this therapeutic aid. In some instances, it makes for complete abandonment of the study on the part of the patient and physician.

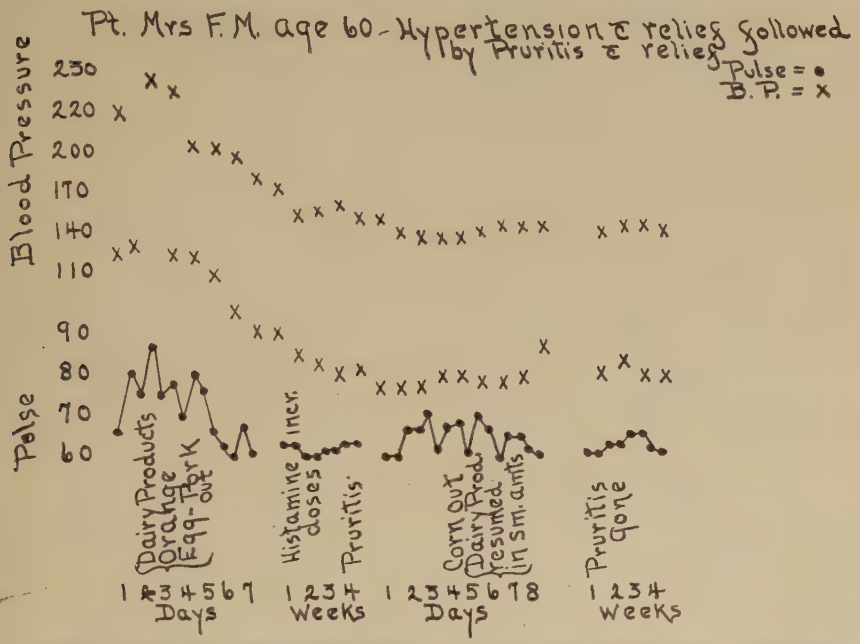


FIGURE 11. Histamine was given in this patient in the hope that dairy products might be reintroduced. After its discontinuance, corn, which had not been considered before, apparently became allergenic, with the perineum becoming the shock tissue.

In brief, the individual has dramatic relief of symptoms, only to be followed weeks later by a recurrence of the original symptoms or possibly a new chain of complaints. It is necessary that a frank discussion with the patient of this possibility be accomplished even before the problem is started. This particular phenomenon is graphically illustrated in charts 8, 9, 10, and 11 in Dr. Coca's book. In some instances, the patient has previously been acquainted with his intolerance to the food. At times, the newly detected allergen is botanically related to the previously indicted food, for example: the sensitivity to wheat and cereals was detected long before cane-sugar sensitivity was encountered.

The aspects of this phenomenon do offer some basis in fact for theoretical

explanation: that is, in many individuals, a non-specific tolerance to the minor allergens has been built up, due to repeated insults by the major allergens. If these major allergens have been eliminated, the production of "H"-body tolerance possibly becomes lessened. This may occur to the point where the body has no non-specific armor against the insults of the minor allergens. Then there occurs a renewal of the original symptoms or a new train of complaints as other organs become the shock tissue. This has been proved by Dr. Coca in his own cases, and I have an interesting corroboration of the same effect in a patient with hypertension. We then started histamine therapy, hoping for a better diet, which gave great aid, only to have a generalized pruritis develop. FIGURE 11 indicates this effect.

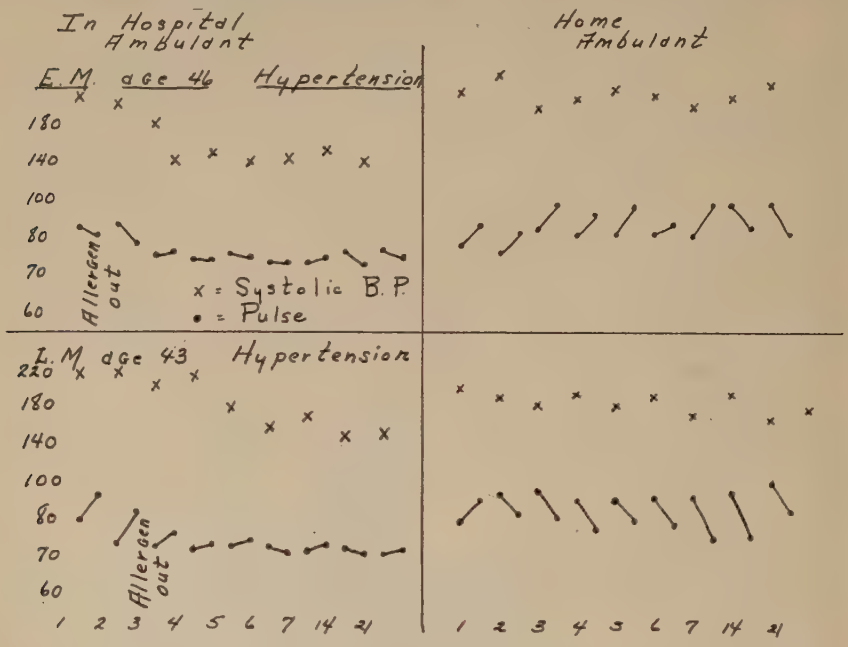


FIGURE 12.

(4) *The Sensitivity to a Large Number of Foods.* This must be proven before the assumption is accepted as correct. Briefly, one must be sure that inhalants and contacts are not entering into the picture. These, too, give an unstable pulse. In these patients with multiple food sensitivity, Coca is a strong exponent of sympathectomy. My patients to date have refused this operation, primarily because mystery of the rationale of interrupting the sympathetic chain is not only too great for them to understand but is too complex for me to explain adequately.

(5) *The Sensitivity to Unavoidable Inhalants Known and Unknown.* This can be illustrated by FIGURE 12 which refers to two patients with hypertension who were perfectly controlled, both in symptoms and in stability of pulse rate, when hospitalized without bed rest. When they were returned

to their homes, however, both symptoms and unstable pulse rates reappeared. In both of these individuals, all of the usual contacts and inhalants have been carefully ruled out.

Before going into the last general topic of this paper, it is well that we carefully evaluate the symptoms which may be ascribed to food allergy. Few of these conditions are regarded by most medical writers as having food allergy for their basis. The proof can only be sufficient if the criteria presented in TABLE 12 are met.

TABLE 12

1. That there is a personal and familial history of a similar condition, or else those illnesses which arearbitrarily placed in the category shown in TABLE 2.
2. That these symptoms have disappeared and reappeared as the foods involved were eliminated and reingested.
3. That with the ingestion of these foods, an accelerated pulse is manifest if extraneous conditions are controlled.

TABLE 13

Irritable colon syndrome	9
Pylorospasm	5
Peptic ulcer	2
Ulcerative colitis	1
Migraine	15
Menière's disease	3
Chronic rhinitis	2
Retinal angiopathy	3
Urticaria	6
Epileptiform seizures	5
Paroxysmal tachycardia	4
Angina pectoris (with EKG changes)	2
Chronic asthmatic bronchitis	4
Acute mental depressions	2
Paralysis agitans	1
Multiple sclerosis*	2
Diabetes mellitus*	3
Emotional instability	5
Hypertension	18
Tinnitus	3
Myalgia	4
Pruritus ani-vulvae	5
Acne	2

I have considered this last criterion because I have learned in several years of practice that the power of suggestion is a very potent weapon in many illnesses, not only those with a pathological basis but those without. It is my opinion that a mild hypnosis, combined with sustained interest on the part of the patient, relative to this new theory, may in itself ameliorate the symptoms.

The Results Obtained

My personal experience has been limited to the symptoms listed in TABLE 13, which I believe to be food allergic by virtue of their disappearance

with food elimination or by the inability to gain a stable pulse when all influences were carefully controlled. In these latter, I regard my failures as being due to either misinterpretation of the trial diet or a sensitivity to such a multiplicity of foods that I could not maintain the patient on that diet. Special consideration of "multiple sclerosis" and "diabetes mellitus" must be given, inasmuch as these are the types of cases which must be followed over the course of several years before one is able to gain an understandable and unbiased opinion as to arrest or cure.

I must emphasize that I cannot assert at this time that all cases falling into the categories mentioned are due to food allergy, but I am becoming enthusiastic enough about the frequency in which they do to use the trial allergy survey on these individuals as a first resort rather than a last resort. I am also agreeably surprised to find that my interpretative ability increases geometrically with practice. As to the results obtained, with a brief discussion as to failures as well as successes, I repeat again that, for several reasons, one must always consider the extent of disability of the patients involved.

(1) Is the patient of relatively stable personality? If not, one always runs the risk of making a "chronic pulse counter" of the individual, with a natural fixation of a cardiac neurosis. The layman associates pulse rate and myocardial reserve as synonymous and parallel situations. Certain individuals have a vasomotor instability which would exist without food in a hermetically sealed room.

(2) Is the patient willing to give up enough of his daily pursuit of pleasure in food ingestion to follow carefully the prescribed program?

(3) Is the patient intelligent enough to realize that no cure is being promised until well after the analysis has started?

(4) If the case is proven to be the result of dietary indiscretion, is the patient willing to forego the particular food or foods involved? Many patients will, during the trial period, lose considerable weight due to the loss of "glamour" in the preparation and serving of the foods and to the loss of extra cellular fluid. These are rather feeble excuses for failures; yet they all exist. I must admit a growing feeling on my part that most people with allergy are emotionally more unstable than those without. Whether the allergy is the cause or the result, I do not know.

Hypertension presents the most interesting possibility, since it may be argued with a certain amount of scientific reasoning that the renal vascular apparatus may well be shock tissue and because it accounts directly and indirectly for such a high percentage of deaths in this country. Coca postulates as follows, following Goldblatt's theory, to a large extent:

(1) "*That ischaemia limited to the kidneys* [author's italics] *may be the initial condition in the pathogenesis of the hypertension that is associated with nephrosclerosis.* If this be true, then renal ischaemia, no matter how produced, should be followed by elevation of blood pressure."

(2) "Hypertension without or with disturbance of renal function, resembling in this respect the benign and malignant types, respectively, in man, can be produced by varying the degree of constriction of the renal arteries."

(3) "The kidney was assumed to be an independent allergic shock organ."

(4) "An hitherto unexplored physical factor in the causation of disease was assumed to be brought into play through the allergic reaction within the kidney. This factor is merely the increased subcapsular pressure caused by the allergic edema. It is easily conceivable that pressure developed in that way could retard the renal circulation sufficiently to provide the essential condition of the Goldblatt experiment. That condition is known to be provided when pressure is applied to the organ externally."

It is also conceivable that this physical factor of allergic subcapsular pressure may play a similar role in the etiology of diseases known to be due to a disturbance of the internal secretion of other organs.

TABLE 14

SIX CASES OF HYPERTENSION TREATED WITH THE METHOD OF PULSE-CONTROLLED TRIAL DIET

Case	*Sex*	*Age*	*Blood pressure*				*Pulse maxima*		*Allergens*
			previous to treatment		*at termination of treatment*		*before treatment*	*after treatment*	
			S	D	S	D			
1	F	63	198	120	124 118	72(3–2) 70(5–25)	98	72	Cereals, cane sugar Beef, pork, milk, nuts, potato, orange, banana, berries
2	M	32	160	110	122 142	84(12–31) 88(2–3)	92	76	Tobacco and other inhalants
3	M	50	160	100	128	88(2–3)	100	76	Cereals, cane sugar, potato, citrus fruit, pineapple, date
4	M	38	150	90	110	70(4–2)	94	78	Cereals, cane sugar, prune fam., squash fam., cabbage fam., tobacco, alcoholic beverages
5	M	40	134	90	106 112 126	74(4–27) 74(5–21) 72(6–5)	116	66	Cereals, coffee, tobacco
6	M	55	145	98	126	74	78	68	

It was pointed out that "if the renal vessels have been permanently narrowed by a chronic inflammatory process following infections (glomerulonephritis), or by the secondary sclerosis of malignant hypertension, this irreversible cause of hypertension would persist after the elimination of any existing food-allergy."

These postulates seem reasonable—certainly as reasonable as any of the theories regarding hypertension, including that of a specific rennin activator. Coca reports the cases illustrated in TABLE 14, with their allergens as described. I have had the opportunity to follow for one year and for six months, respectively, the individuals shown in TABLES 15 and 15a. These have remained very well controlled from the standpoint of objective findings as well as subjective symptoms.

It is also of interest to note that, with the falling pressure, none of these

patients has had evidences of impaired coronary circulation, which so often occurs when so-called specific medication to lower the pressure has been used.

These cases offer an interesting corollary to the success which Dr. Kempner of Duke University has achieved. With his rice and fruit juice diet, he has had good results in about sixty per cent of his cases. Certainly, it is within the realm of possibility that in his cases the elimination of the food allergen is responsible.

TABLE 15

Name	*Age*	*Previous B.P. (6 or more readings average)*		*Present B.P. (10 or more readings average)*		*Allergens*	*No. of months followed*
		S	D	S	D		
Mrs. P. M.....	52	190	110	140	86	Beef, peas, str. beans, tomatoes, spinach	16
Mrs. S. R.....	64	220	130	160	90	Eggs, celery, citrus fruit, apples	15
Mrs. M. M.....	58	190	110	150	84	potatoes, beef, peas, str. beans	15
E. P.....	40	166	100	142	84	citrus fruit, cane sugar, fish	15
Mrs. J. F.....	47	180	120	146	80	eggs, pork, coffee, chocolate, chicken	15
J. D.....	38	158	100	130	76	chocolate	15

TABLE 15a

Patients Followed 6 Months Minimum

No. of patients	Average diastolic pressure before allergens removed	Average diastolic pressure after allergens removed
18	102	86
Total no. of hypertensives treated	**Those now with diastolic B.P. below 100**	**Percentage**
34	22	64/7

Until, however, actual food sensitization can be given the laboratory animal and a careful and accurate measurement of blood-flow through the kidneys can be ascertained before and after the allergic insult, all theoretical considerations of the exact mechanism involved will of necessity remain in the realm of conjecture. One is still forced into the position of stating, "My theory is as good as yours until proven otherwise."

Coca believes, and I certainly agree, that if kidney damage is such that nitrogen and dye retention has already occurred, there is little use to hope that regeneration of destroyed cortical substance can be accomplished.

Even in such patients, however, I have had the gratifying experience, in two cases, of having laboratory findings change as well as clinical symptoms. That some of the damage was transitory, due to vascular spasm or fluid pressure, is my only hypothesis. TABLE 16 illustrates this point. It is my feeling that Coca's theory can be substantiated in a rather high number of hypertensives. This only when the physician, as well as the patient, is willing to subject himself to the tedious processes described.

That food allergy will cause arterial spasm is an established fact. This statement is made in light of two illustrative cases which I saw in consultation with an opthalmologist. These two patients suffered rather sudden loss of vision, both showing marked retinal angiopathy, one associated with

TABLE 16

Name	*B.P.*	*Urine*	*Chemistry*	*B.P.*	*Urine*	*Chemistry*
	(*before allergens out*)			(*after allergens out*)		
Mrs. E. L., age 36. Dizziness, headache. Exertional: dyspnoea, heart-conscious	250/140 230/136	Sp. gr. 1004 Alb—Tr Micro 3–4 hyaline 1–2 granular HPF	NPN—48 Urea N—30 P.S.P. 1 hr.—20% 2 hr.—22%	160/88 158/84 158/82	Sp. gr. 1016 Alb—0 Micro Amorphurates only Only occasional	NPN—32 Urea—18 P.S.P. T 1 hr.—40% 2 hr.—16% headache now
Mrs. S. R., age 62. "Palsy," dizziness. Exertional: palpitation, angina, dyspnoea	210/130 220/134	Sp. gr. 1006 Alb—+ Micro 7–8 hyaline 4–5 granular HPF	NPN—52 Urea N—32 P.S.P 1 hr.—28 2 hr.—18	170/90 172/88 168/88	Sp. gr. 1014 Alb—spt Micro 1–2 hyaline HPF Dyspnoea only—and with marked exertion	NPN—40 Urea N—20 P.S.P.J 1 hr.—40 2 hr.—20

TABLE 17

15 CONSECUTIVE PTS. c̄ GASTRO-INTESTINAL COMPLAINTS

X-ray exam: judged neg. for organic pathology	8
X-ray exam or clinical and lab. exam. judged negative for organic pathology	11
Positive x-ray and clinical findings for organic disease	4
Number of patients well after elimination of allergens	10
Percentage of functional cases cured without medication	90.9%

a hypertension, the other with a normal blood pressure. They were both hospitalized for careful study and were both given multiple histamine doses in glucose saline. Their objective and subjective findings cleared almost immediately. This was followed by a careful study of possible offending foods, and after six months both patients, following elimination of the foods involved, had normal vision and normal opthalmological findings.

Of those patients with symptoms referable to the gastrointestinal tract, it is seemingly becoming more and more apparent that the so-called "irritable colon syndrome" is in reality an allergic expression on the part of the digestive apparatus. TABLE 17 shows the consecutive number of cases seen with gastrointestinal symptoms, the laboratory findings, and the results. This is not a large series, but it must be remembered that, in private practice, a diversified group of people are seen and a complete

diagnostic survey to exclude all organic possibilities is sometimes difficult to accomplish because of monetary consideration on the patient's part. Naturally, it is within the realm of possibility, as Coca has suggested to me in personal communication, that all disordered functions of the digestive system may have allergy as their original basis.

Diseases of the nervous system, as previously illustrated, especially those in which we have no other readily available etiological explanation, certainly open the door in a small way into a fascinating and constructive train of thought. My personal experience with multiple sclerosis is not of sufficiently long standing even to be acceptable; yet in two patients, followed for six months, there has been a complete arrest of symptoms. Epileptiform seizures, as indicated by Coca, have been greatly lessened in severity and frequency and in some cases abolished. My experience so far is not as completely satisfactory as his. The best results I have obtained are in those individuals in whom the aura of these attacks is headache. I am quick to

TABLE 18

Name	*Age*	*Average freq. of attacks*	*Grand mal*	*Frequency*	*Medication as before*
B. B.....	24	3 times weekly	+	3 times wkly.	+
L. C.....	19	5 times yearly	+	2 times in 15 mos.	+
L. N.....	34	2 times monthly	+	1 time in 4 mos. Known diet. indiscretion	0
M. M.....	62	2 times monthly	+	1 time in 6 mos.	0
C. T.....	64	3 times weekly	+	2 times in 10 mos.	½ dosage Dilantin S.
L. S.....	26	3 times daily	0	3 times daily	+
E. P.....	58	4 times monthly	0	1 time in 6 wks.	No medication

admit, however, that I have had no sympathectomies performed. TABLE 18 shows the epileptics seen by me, with the results obtained.

Coca presents some very definite investigative figures on individuals with frank psychosis. To my knowledge, no concerted efforts have been made to follow up these acutely interesting conjectures. Certainly, the results accomplished in those people with emotional instability, tinnitus, and Meniers Syndrome and, in one case only, the relief from the distressing symptoms of paralysis agitans make the investigator rather enthusiastic in his belief that the central nervous system may also be shock tissue.

The sensitization of the cardiovascular apparatus to allergens, in the opinion of Coca and myself, is well supported. Whether this be through the mechanism of the autonomic nervous system or by direct action on both the conduction system and the arterial caliber is difficult to evaluate. I refer primarily to angina pectoris, paroxysmal tachycardia, and neurocirculatory asthenia.

The inheritance factor of idioblapsis is unquestioned if one is willing to "go along" with Coca in the acceptance of the large number of symptoms which he and I regard as arising from idioblapsis. Statistical support for

his contention is contained in his careful survey of school children in his own community, and, to my mind, it is well supported by the questionnaires which we in our own group utilized. Similar interesting observations suggesting the 100 per cent incidence of a familial background have been recorded by others.

A summary in any paper having for its main thesis a group of another's postulates is difficult. However, I should like to reiterate those points which I believe warrant serious and concentrated study on the part of all interested physicians. They are as follows:

(*1*) There is apparently a fifth category of allergic illnesses, named by Coca, "idioblapsis."

(*2*) This category has a definite symptomatology.

(*3*) The allergenic material or food causes an acceleration of the pulse, and a careful study of the pulse rate is the only accurate means of identifying the offending articles.

(*4*) Failure of identification is based primarily on the physician's inability to interpret the effect of the latent period, the recurrent reaction, the differentiation of major and minor allergens, the depression of shock tissue with repeated insults, and, finally, the sensitivity to a large number of foods or unavoidable inhalants.

(*5*) A rather large group of symptoms referable to almost all of the bodily systems have been presented with statistical data to support the contentions that they are of allergic origin.

(*6*) The possibilities for further investigation are almost inconceivable in their scope, and further corroboration of this fascinating subject is earnestly sought.

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FAMILIAL NONREAGINIC ALLERGY AS A PREDISPOSING CAUSE OF COMMON COLD

By Arthur P. Locke

Zonite Products Corporation, New Brunswick, New Jersey

This is a report of an investigation begun sixteen years ago at St. Luke's Hospital, Chicago, and carried from there to the Western Pennsylvania Hospital, Pittsburgh, and to Stephens College, Columbia, Missouri. It began as a search for an answer to the question: Is there any way of telling, beforehand, when a group of animals is given an infection of borderline virulence, which animals probably will live and which probably will die? The answer to this question led the way to a second: Is there any way of telling, beforehand, when a group of persons has been exposed to common cold, which persons probably will develop common cold and which will not?

This second question is our objective. But, first, what is known about susceptibility to infection, in animals? A great deal was known, even sixteen years ago. Many factors had been found that actively lower resistance to infection. Among them were shock, and injury producing shock, poisoning, starvation, endocrine deficiency, and exhaustion.

During anaphylactic shock in dogs, Boone, Chase, and Brink[1] had observed a lessened resistance to invasion from foci in the intestines. Blood cultures persisting for hours beyond the time normally observed had been found by Weisberger[2] and by Burn, Chandler, and Hartshorn,[3] in rabbits injected intravenously with streptococci, during anaphylactic shock. Robertson and associates[4] had shown that the resistance to pneumococcal invasion can be lowered by morphine. We[5] had found that morphine in massive dosage can be so effective an opener of the doorway to infection that infections can be established in rabbits with a type of pneumococcus not normally invasive. Vitamin C depletion, to the point of severe scurvy, was found by McCullough[6] to have a related effect in the guinea pig. Pickrell[7] found that alcohol in high dosage so lowered the capacity for resistance as to lessen even the protection given by antisera.

These different ways of lowering resistance had one factor in common. They interfered with the ability of the animal to function efficiently. Particularly, they interfered with the ability to keep warm. It is common knowledge what shock can do to body temperature. Morphine and ether, in amounts sufficient to lower resistance to infection, also lower the body temperature.[4,7] This tell-tale indication, that lowered resistance to infection may go hand in hand with lowered resistance to chilling, and to other emergencies with which life can be confronted, was explored further.

A method was worked out for determining ability to warm up after chilling.[8] Rabbits were used. They were chilled in cool water until the rectal temperature had fallen to 96. Then they were dried and allowed to warm up spontaneously. The unit adopted was the time required for a rectal temperture rise from 96 to 99—the *warming time*. The temperature rise was plotted on chart paper as in the examples in FIGURES 1–4.

TABLE 1 compares the response of two rabbits to a test chilling and to a later test of ability to dispose of intravenously injected pneumococci. The rabbit that had made the faster recovery from chilling had a blood culture of 2 pneumococci per ml. one hour after injection and was negative at the end of three hours. No fever developed, and no weight was lost. The rabbit survived. The rabbit that had made the slower recovery from chilling was slower also at the task of disposing of injected pneumococci. The count had decreased only to 44 at the end of the first hour. Multiplication had begun and the count had become increased to 244 at 3 hours. Fever developed and death occurred within 48 hours.

A larger series was studied to determine whether this parallel between the rabbit's ability to respond quickly to the demands of chilling and its

TABLE 1

RATE OF TEMPERATURE RECOVERY AFTER A TEST CHILLING, AND RATE OF REMOVAL FROM THE BLOOD STREAM OF INTRAVENOUSLY INJECTED TYPE I PNEUMOCOCCI

Minutes required for spontaneous rise of rectal temperature, after chilling, from 96 F to 99	*Number of pneumococci demonstrable, per ml. of blood, at the indicated hour*		
	0	1	3
35	114	2	0
60	100	44	244

TABLE 2

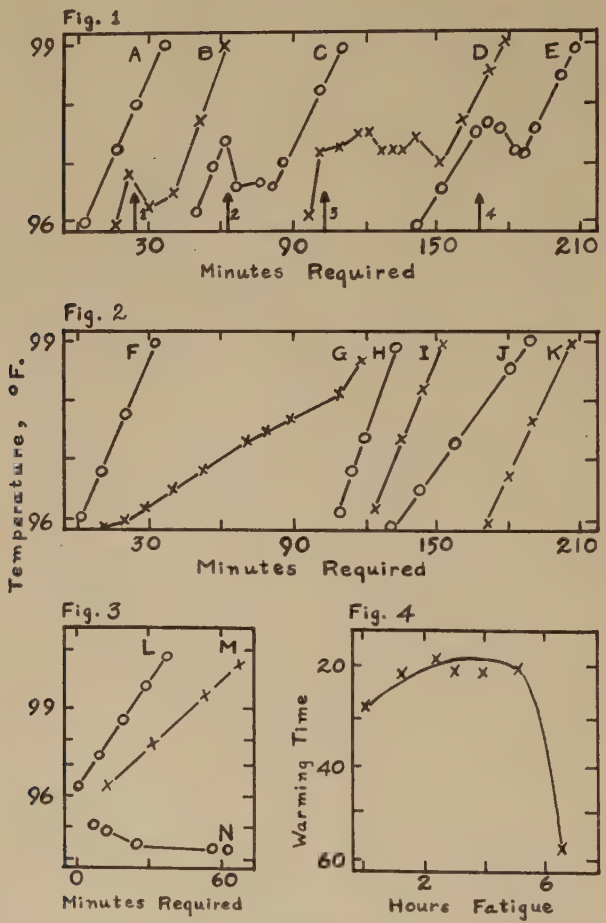
PER CENT SURVIVAL FOLLOWING INTRAVENOUS INJECTION OF TYPE I PNEUMOCOCCI

Warming time at time of infection	*Number of rabbits studied*	*Per cent surviving*
Less than 35	11	82
35 to 45	21	47
More than 45	9	0

ability to respond quickly to the demands of infection was a matter of chance or an indication of general principle. TABLE 2 summarizes a series of comparisons of warming time and resistance following intravenous infection in 41 rabbits. A sufficient number of virulent, type I pneumococci was injected to produce one death, roughly, in every two. A total of 19, out of the 41, survived. The rabbits had been tested for their reaction to chilling two days or longer before their test for reaction to infection. Eighty-two per cent of those which had been found to have a fast warming time survived, as compared with zero per cent for those which had been found to have a slow warming time. The rabbits which lived were those which disposed of their infections before those infections could get an overwhelming start. The rabbits which died were those so slow in disposing of their infections that overwhelming multiplication set in before the job of getting rid of the

bacteria could be completed. Also, this difference in speed of disposing of a test infection was paralleled by the earlier determined difference in speed of temperature recovery after chilling.

FIGURE 1 shows what happens to the warming time during shock. Rabbit A is the control. Shock was produced in rabbit B by an injection of his-



FIGURES 1–4.

tamine[8] at the time marked by the arrow, following which temperature recovery stopped for 20 minutes. Anaphylactic shock had a related effect in rabbit C. Pitressin produced a similar transient cessation of temperature rise in rabbit D.

This action of anti-diuretic pitressin is of special significance. Nedzel has reported that injections of pitressin can lower resistance to infections of a type associated with endocarditis.[20] Coca[17] has called attention to the rapid increase of weight which sometimes is noticed at the onset of allergic

headache and the equally rapid loss of weight as the attack passes off and states that "Some observers have reported that the loss of weight has been associated with an increase in the excretion of urine. . . ." Water retention, followed by diuresis, also comes into the common cold picture.

F, G, and H, in FIGURE 2, describe the warming time before, during, and after action of morphine in depressant dosage.[8] Rabbits M and N were subjected to a six-day fast. M was a healthy rabbit, free of discernible infection. N had infected wounds. The warming time is lengthened by prolonged starvation, and the effect is more serious in an infected rabbit than in one free of infection.

The first effect of progressive fatigue, as shown in FIGURE 4, is to shorten the warming time. It produces stimulation. After exhaustion, the warming time lengthens to an hour or more. Fatigue brings on exhaustion only slowly in healthy rabbits but rapidly in rabbits harboring infection. The sensitivity to shock also is increased when the warming time has been excessively shortened by fatigue or other stimulation.[9]

The 33 rabbits in TABLE 3 were given a shock injection of histamine by vein which killed approximately one-half.[9] Eighty per cent of those with

TABLE 3

WARMING TIME AND SUSCEPTIBILITY TO HISTAMINE SHOCK

Warming time at moment of shock injection	*Number of rabbits tested*	*Per cent developing fatal shock*
16 to 21	10	80
22 to 30	17	47
More than 33	6	0

warming times between 16 and 21 developed fatal shock, as compared with zero per cent for those with warming times longer than 33. It can be seen, with this observation, where the facts are leading. The rabbits with a slow warming time are unable to *keep up* with the demands of infection. The rabbits with too fast a warming time are unable to withstand shock. Natural infection requires resistance not only against the growth of the invading organisms but, also, against those products of their growth which cause effects related to shock. This means that the warming time range associated with most effective resistance to prolonged infection, in the rabbit, must be neither too slow nor too fast, but in between.

The rabbits in TABLE 4 received an injection of type I pneumococci into the skin, creating a focus in which the pneumococci could multiply out of direct reach of the defenses available to the blood stream.[9] Prolonged resistance was called for. Only 6 out of the 50 were able to survive. These 6 which survived had warming times that were neither too fast nor too slow, but in between. Our first question had been answered. One *can* tell, beforehand, out of a series of rabbits given an infection of borderline virulence, which ones have the greatest chance for survival and which ones have the least.

Before the investigation could be extended from rabbits to man, three further questions had to be answered. (1) Does common cold represent an infection of borderline virulence that can be utilized as an index of resistance in the way that resistance to pneumococcal infection was used in the rabbit? (2) Do differences exist between different individuals, in susceptibility to common cold? (3) Can tests be made on human subjects giving the information that is given by the warming time test for the rabbit?

The common cold is considered, by the writer, to be an infection of a community. The reason is this: when common cold is viewed for its effect on a community, a definite, reproducible pattern can be seen.[10] When it is viewed for its varied effect on the individual persons making up that community, it is neither definite nor reproducible. The common cold is a clinical entity, running a characteristic course[11] in the community as a whole and having certain, well-known common effects on the individual at onset, but it varies from individual to individual in the sum total of pathogens actively involved and in the complexity of the infection set up.

TABLE 4

PER CENT SURVIVAL FOLLOWING INTRADERMAL INFECTION WITH TYPE I PNEUMOCOCCI

Warming time at time of infection	*Number of rabbits studied*	*Per cent surviving*
16 to 20	3	0
21 to 29	11	9
30 to 35	14	29
34 to 40	9	11
More than 40	13	0

Marked differences are known to exist in susceptibility to common cold. Paul and Freese[12] saw this, in a study made in Spitzbergen. An outbreak of common cold had followed the arrival of a boat. It spread in the characteristic way until it had involved almost all the people there. However, a small number who, in the words of Paul and Feeese "were constantly exposed and who were under close scrutiny failed to show susceptibility. . . ." The proportion of persons failing to show susceptibility was about 1 in 10. Brown,[13] in a more recent report from the Aleutian Islands, found that about one in eight, in his group, remained free of common cold. That is about the proportion found in our studies in Pennsylvania[14,15] and Missouri[11,16] and by Coca in New Jersey.[17]

The development of a test giving information on human subjects, like that given by the warming-time test for the rabbit, presented difficulties that required five years for solution.

One of the tests evolved measured the reaction to the respiratory demands of exercise.[14] A preliminary medical examination was given, and record was made of the height, weight, and vital capacity. Work was begun with the arms and legs, on an exercising machine. During the work interval, a record was kept of the breathing and use of oxygen. Following com-

pletion of a satisfactory test, the subject was asked to report weekly as to freedom from common cold. At the end of the year, the tests and the colds record were compared. The subjects who had had colds most frequently were, for the most part, those who had responded to the test like the too fast and too slow warming rabbits. The subjects with the fewest colds had made an in-between type of response.[14] Two additional groups were studied to make sure that this relationship was not accidental. The findings are summarized in TABLE 5.

Seventy to 82 per cent of the persons with responses to the exercise test, like those found the year before for those with fewest colds, had a better than average colds record. A better than average colds record was made by only zero to two per cent of those with responses clearly divergent from the range found to be optimum the year before.[14]

A further test measured the reaction to inhaled carbon dioxide.[15] After a preliminary examination and measurement of the height and weight, the subject was asked to relax in a reclining position. The blood pressure and

TABLE 5
RESPONSE TO EXERCISE TEST AND SUBSEQUENT COLDS RECORD

Response to test	*Year*	*Number of persons*	*Per cent with a colds record*	
			Better than average	*Worse than average*
Optimum*	1936–7	33	70	0
	1937–8	21	82	0
Clearly divergent	1936–7	58	2	45
	1937–8	22	0	32

* As indicated by a preliminary series, studied through 1935–6. Borderline groups omitted. Total number of subjects: 1935–6, 87; 1936–7, 155; 1937–8, 68.

pulse were taken and a mask was fitted over the face and connected to a device tracing the frequency and depth of breathing. This tracing was examined and was seen to be within the normal range for the observed height and weight while breathing ordinary air. Then a valve was turned, supplying air containing five per cent of carbon dioxide. In some of the subjects, the added carbon dioxide only slightly increased the rate and depth of breathing. In others, the carbon dioxide caused the breathing to become greatly increased. Still others made an intensity of response that was in between.

A second test was made, one to two weeks later. Each subject was questioned weekly as to freedom from common cold. At the end of the year, the tests and the colds records were compared. The subjects who had had colds most frequently were those, for the most part, who had made only a slight or else a very pronounced response to the carbon dioxide. The subjects with the fewest colds had made a response of intermediate intensity. A second series was studied the following year.

Table 6 summarizes the observations for the second year. Sixty-five persons had been tested and had faithfully reported their common cold status. Of these, only 16 had made the response to carbon dioxide which had been found, during the preceding year, to be associated with lowest incidence of common cold. Seventy-five per cent of this group of 16 remained cold-free for intervals of 4 months or longer. The average number of colds was 1.6. In the contrasted group, who made the responses to

Table 6

Response to CO_2 Test and Subsequent Colds Record, 1939–40

*Response to CO_2 per cent divergence from optimum**	*Number of persons*	*% remaining cold-free for 4 months or longer*	*Average number of colds per person*
0 to 5	16	75	1.6
6 to 10	30	40	2.7
More than 10	19	21	3.7

* As indicated by a preliminary series, studied through 1938–9.

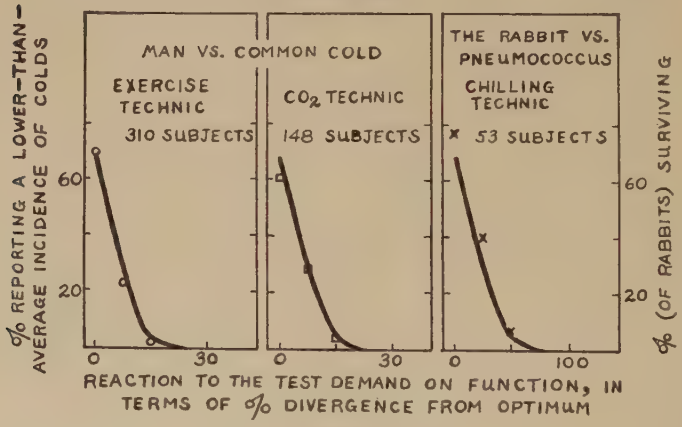


Figure 5.

carbon dioxide diverging most widely from optimum, only 21 per cent remained cold-free for 4 months or longer, and the average number of colds per person was 3.7.

If one takes the per cent divergence from optimum in the warming time as an index of decrease in functional efficiency for the rabbit, the per cent divergence from optimum in the responses made to the exercise test and to the carbon dioxide test as indices of decrease in functional efficiency for man, the number of colds as an index of resistive efficiency for man, and the per cent survival following pneumococcus infection as an index of resistive efficiency for the rabbit, a striking parallelism is apparent (figure 5).

This parallelism suggests that common cold may become established most frequently in those of us who, like the too slow and too fast warming rabbits, are unable to maintain a continuously efficient defense against infections of borderline virulence.

What is the cause of this handicap? What possibly can happen to the large fraction of the population that is subject to common cold, that is sufficiently frequent and sufficiently severe to account for it?

Before our search for an answer to these questions had gone very far, a paper appeared by Coca[18] describing a type of allergic reaction to ingested food that met all of the test requirements. It affected a percentage of the population of about the same size as is affected by common cold. It was apt to affect its subjects frequently, so as to make them repeatedly vulnerable. It could be seen that, during a period, however brief, that the digestive tract might be reacting as a shock organ to an ingested allergen, the doorway might be thrown as widely open to common cold as it had been found to be opened to experimental infection in rabbits during periods of reaction to anaphylactic shock.

Coca had found that, when persons with a nonreaginic food allergy eat the food or foods that provoke the allergy, a sharp rise in pulse rate occurs which exceeds the rise produced by foods which do not provoke the allergy.[19] The persons giving this pathognomonic, pulse-rise indication of disturbed adjustment and impaired efficiency following the ingestion of a specifically trouble-making food were found to have histories, generally, of one or more of the following accessory indications, in recurring, cause-and-effect relationship with the food source: headache, hives, indigestion, diarrhea and constipation, canker sores, nervousness, and tiredness.

There are two striking things about this list of accessory symptoms. First of all, they are symptoms commonly and frequently experienced. Coca has found some degree of nonreaginic allergy in 75 to 80 per cent of the groups that he has examined. Anything affecting 75 to 80 per cent of us to an extent which invites common cold must be both common and frequently experienced. In this field of allergy and common cold, we must realize that we are looking for things that affect almost all of us—things that *are* common and frequent, but none the less important when properly considered. The second striking thing about this list is its length. Disturbed adjustment and impaired efficiency can be far-reaching, complex, and varied in final result.

Coca saw how closely the percentage of persons with nonreaginic allergy approaches the percentage susceptible to common cold. He had, shortly before, made a survey of the frequency of common cold among his associates and had, ready for study, a group of about 52 persons who had not had a cold for 3 years. Against this, he balanced a group of 51 with a history of at least one cold annually. The two groups were questioned for indications of the presence of nonreaginic allergy in themselves and in their families.

Ninety-two per cent of the colds-susceptible group had two or more indications of a background of nonreaginic allergy. Only 12 per cent of the nonsusceptible group was so affected. This striking difference showed

clearly the frequency with which symptoms indicative of nonreaginic allergy are found in persons subject to common cold and the infrequency with which they are found in persons not subject to common cold.

A confirmation of Coca's findings was obtained at Stephens College, Missouri.[16] Six hundred students were questioned there by an examiner trained by Dr. Coca but working under independent direction. The findings were checked against information secured from the parents and by a series of second interviews by a referee observer.

The findings of the questioner trained by Dr. Coca paralleled closely the findings obtained by the referee observer. Headache, recurring in a cause-and-effect relationship with food, was found in 57 to 67 per cent of the students questioned. Tiredness, nervousness, dizziness, constipation, indigestion, urticaria, and canker sores were found in 13 to 37 per cent. The average number of symptoms found, per student, was 3. Seventy-nine per cent of the students had 2 symptoms or more. This figure, 79 per cent was close to the figure of 75 to 80 per cent found by Coca in New Jersey'

TABLE 7

NUMBER OF COCA'S 11 SYMPTOMATIC INDICATIONS OF NONREAGINIC FOOD ALLERGY* IN THE CHILDREN OF PARENTS WITH AND WITHOUT MORE THAN MINIMAL EVIDENCE OF SUCH HANDICAP

Number of parents	*Number of children*	*Number of symptoms*		*Per cent of the children with two symptoms or more*
		Father	*Mother*	
284	222	less than 2	less than 2	19
70	57	2 or more	less than 2	37
206	165	less than 2	2 or more	45
238	199	2 or more	2 or more	63

* As reported by the parents both for themselves and the children.

The information obtained from the parents tended to be less complete than that obtained directly from the students, but did have the value of presenting that information against a background of equivalent information about themselves and the sisters and brothers (TABLE 7).

Passing downward, in TABLE 7, from a combination of father and mother, neither of whom had two or more indications of the presence of nonreaginic allergy to a combination of father and mother both of whom had two or more such indications, we also pass from a figure of 19 per cent for the children having 2 indications or more to a figure of 63 per cent. The significance of this observation is modified by the common origin of the figures compared, but not seriously so. It is exactly the type of relationship to be expected from Coca's classification of nonreaginic allergy as familial.

Each of the symptoms questioned for, when lined up with the number of colds developed during the following year, could be seen to be associated with a larger number of colds than was observed in the absence of symptoms (TABLE 8). The group with no symptoms, no hay fever or asthma and a response to the Flack test which was neither excessive nor subadequate,

had an average of one cold for the year. (The Flack test had been used in an exploratory way as an index of efficiency.) The corresponding group with two symptoms or more had an average of 1.8 colds for the year.

Addiction to smoking was found to be a factor further affecting the results. Both the effect of smoking and the effect of an excessive or subadequate response to the Flack test were confirmed in a further investigation the following year.[11] When the figures were sifted for these complicating factors, and when smoking and unfavorable response to the Flack test were given a weight of two symptoms each, a clear parallel was found between number of colds for the year and number of sources of allergic or other handicap. The group with the largest handicap had almost four times as many colds for the year as the group with smallest handicap.

TABLE 8

SYMPTOMATOLOGY AND COLDS INCIDENCE; SUBJECTS FREE OF HAY FEVER AND ASTHMA

*Symptom**	*Flack test pulse rise between 6 and 24*		*Flack pulse rise less than 6 or more than 24*	
	No. of persons	*Avg. no. of colds*	*No. of persons*	*Avg. no. of colds*
None presented	14	1.00 ±.17†	10	1.30 ±.27†
One only	31	1.06 ±.11	18	1.83 ±.16
More than one	155	1.80 ±.07	107	2.14 ±.10
Hives	57	1.9	42	2.6
Headache	128	1.8	88	2.3
Indigestion	42	1.9	34	2.3
Canker sores	75	1.7	59	2.2
Dizziness	35	1.9	26	2.5
Constipation	62	1.9	33	2.1
Nervousness	39	2.0	30	2.7
Tiredness	50	1.7	43	2.7

* As reported by examiner I. G.
† The probable error, Peter's formula.

The probability would seem to be substantial that the entity described by Coca as familial nonreaginic allergy does exist, to an extent affecting somewhere near three-fourths of us and to a degree providing a trigger, touching off intervals of inability to cope with emergencies, that may be in the background of many disease pictures. Common cold is only one of many infections by pathogens of borderline virulence that may have a beginning or a recrudescence during an interval of food-allergic reaction.

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THE ANTIALLERGIC ACTION OF SYMPATHECTOMY*

By Arthur F. Coca

Lederle Laboratories Division, American Cyanamid Company, Pearl River, New York

To the best of my knowledge, the operation of sympathectomy as a consciously antiallergic measure was first performed on myself by Dr. Laurence Miscall at my request. As I was aware, the operation had been successful in some of the cases in which it had been employed upon an empirical basis for the reduction of hypertension. I think my knowledge of that fact was the most persuasive consideration impelling me to the operating table, because I had become convinced of the primarily allergic nature of hypertension.

My own history illustrates very well the nature of the antiallergic action of the operation, as well as its limitations. Also, in general, it contributes to the very important practical conclusion that the maximal antiallergic effect is obtainable with the least transverse section of the main sympathetic chain that can be permanently maintained.

Through many years of trial and error, at first without, later with the use of the criterion of specific tachycardia, I had found myself clinically allergic to all available foods excepting beef. In ignorance of Stefansson's demonstration of the indispensibility of fat for a man's nutritional requirement on an exclusive diet of meat, I ate only lean beef and rapidly lost both weight and appetite.

TABLE 1 presents the more common of my allergenic foods in approximately the chronological order of their identification. For some months after they were first identified as allergens, the foods listed in the second and third columns could be eaten without symptoms at one or two-week intervals. None of these was being eaten when the foods in the fourth column began to cause symptoms. The latter are in heavy type to indicate that, shortly after daily subcutaneous injections of histamine were begun, all three of them could be restored to the diet without any reaction.

In May, 1942, Dr. Miscall performed the first stage of the sympathectomy (Crile). Three right lumbar ganglia and the right half of the celiac ganglion were removed, and 2.0 cc. of absolute alcohol were injected into the left half of the celiac ganglion. Three and one-half months later, the second stage of the Crile operation was carried out.

After the first operation, the following symptoms disappeared without need of any restriction of the diet: migraine, gastric pain, gastrointestinal bleeding, constipation, hemorrhoids, chronic rhinitis, and lapses of memory. There remained tiredness, neuralgia (occipital and sciatic), with occasional numbness of ulnar nerve distribution, and hypertension (up to 190/122) and, also, canker sores, heartburn, and mild conjunctivitis.

It is noteworthy that the residual symptoms were not perceptibly modified by the second operation. This observation caused me, thereafter, to recom-

* Much of this material has been published in the Annals of Allergy, March–April, 1947, and in Familial Nonreaginic Food Allergy, Charles C. Thomas, publisher, Springfield, Ill.

mend only the most conservative procedure—removal of only three lumbar ganglia on one side. With one exception, all of my operative patients were so treated, the exceptional patient having had a left cervical sympathectomy.

Several months elapsed after the operations on myself and on the several patients who followed me before I realized the improbable and still inexplicable fact that sympathectomy abolishes not all-or-none of the sensitivities but, selectively and unpredictably, the sensitivity to *certain* of the allergenic foods.

Table 2 presents again the list of my food allergens. But, this time, the items in heavy type are those which, since the operation, have been eaten in unlimited quantity without any allergic reaction. It is seen that, whereas

Table 1*

wheat	rice	potato	**milk**
pork	oat	peach-plum	**fowl**
lemon	tomato	fish	**banana**
corn	lettuce	onion	
sugar-cane	cabbage (fam.)	spinach	
sweet potato	chocolate	carrot	
apple	orange	beet	
	pea-bean	grapefruit	
	peanut	egg	

* Showing the nonselective abolishment of the sensitivities to the three weak food allergens in patient A. F. C. under daily injections of histamine diphosphate. The items in heavy type could be eaten without lergic reaction during the period of the injections.

Table 2*

wheat	rice	potato	milk
pork	oat	peach-plum	
lemon	**tomato**	**fish**	**fowl**
corn	lettuce	**onion**	
sweet potato	cabbage (fam.)	spinach	**banana**
apple	**chocolate**	carrot	
sugar-cane	orange	beet	
	pea-bean	grapefruit	
	peanut	**egg**	

* Showing the selective abolishment of food sensitivities through sympathectomy in patient A. F. C. The items in heavy type have been eaten without allergic reaction since the operation. These food-allergens are arranged in groups in the order of their recognition as excitants and/or their elimination from the diet.

the sensitivity to some of the major allergens has been abolished, that to some of the weaker ones and even to one of the weakest—milk—persists. Evidently then, the sympathectomy did not result in a nonspecifically increased tolerance to the H-substance, such as can be induced by injections of histamine. The selectivity of the effect of the sympathectomy recalls, rather, the *specificity* of the sensitivities concerned. This astonishing conclusion seems so important practically, as well as theoretically, that I should like to support it with other illustrations.

Table 3 shows the unselective tolerance toward the weaker allergens in patient C. T., induced by daily repeated injections of histamine diphosphate:

This was a young woman employed by the Metroplitan Life Insurance Company, where a diagnosis of "nervous and emotional instability—incurable" had been made. Her chief symptoms were severe dizziness, depression, hysteria, abnormal tiredness, "fluttery heart" (probably extra systoles), neuralgia, and constipation. The foods listed in the first column are those first identified as allergens in this case. In the seven months following the elimination of those foods from the diet, the patient was free from her allergic symptoms.

Her symptoms then began to recur and again disappeared on avoidance of the foods listed in the second column (group 2). A few weeks later, her sensitivity to the weaker allergens began to emerge, beginning with cane sugar, and she gradually lost weight. Within a week after the injection of histamine were begun, she found herself able to eat the foods marked by heavy

TABLE 3*

Group 1 (major)	*Group 2 (medium)*	*Group 3 (minor)*
beef	**tomato**	**sugar-cane**
wheat	rice	**potato**
orange	rye	**banana**
grapefruit	corn	**strawberry**
lemon	oat	**aluminum**
plum	coffee	
	onion	

* Showing the nonselective abolishment of the sensitivities to the entire "minor" group of allergens and to one of the "medium" group in patient C. T. under daily injections of histamine diphosphate. The items in heavy type could be eaten without allergic reaction.

TABLE 4*

Group 1 (major)	*Group 2 (medium)*	*Group 3 (minor)*
beef	tomato	**sugar-cane**
wheat	**rice**	potato
orange	**rye**	**banana**
grapefruit	**corn**	**strawberry**
lemon	**oat**	**aluminum**
plum	coffee	
	onion	

* Showing the selective abolishment of food-sensitivities with sympathectomy in patient C. T. The items in heavy type have been eaten without allergic reaction ever since the operation. Note that the sensitivity to tomato and potato, which had been suppressed by histamine-injections, remained unaffected by sympathectomy.

type without reaction, and she regained her lost weight at the rate of $2\frac{1}{2}$ pounds weekly. Tests of some of the other foods were followed by recurrence of her characteristic allergic symptoms, including dizziness.

This experience, together with the corresponding one in my own case, teaches that the nonspecific antiallergic tolerance obtained by injections of histamine is quantitatively limited to protection against the weaker (minor) food allergens.

TABLE 4 presents again the list of the original food allergens of C. T. The items in heavy type are those that have been eaten since the sympathectomy without any allergic reaction. In this case also, the antiallergic effect of the operation is seen to be selective. Although sensitivity to three of the

major allergens was abolished, that to the much weaker allergen potato remained. Moreover, the sensitivity to three still weaker food allergens that had not been previously detected now emerged: namely, chicken, egg, and tea. To these was added some chemical allergen of the local water supply.

The third case is different from the two just described, inasmuch as the pulse-dietary analysis conducted previous to the sympathectomy failed to disclose a single nonallergenic food. TABLE 5 shows the record for one day

TABLE 5

C. W. PULSE RECORD PREVIOUS TO SYMPATHECTOMY

Time	*Pulse*	*Diet: symptoms*	*Time*	*Pulse*	*Diet: symptoms*
July 25, 1942			*July 27, 1942*		
B.R.	79		B.R.	72	tooth-paste, grapefruit
B.	93	tomato, eggs, pumper-	B.	102	
30′	96	nickel, milk	30′	90	
60′	102		60′	93	
90′	100		90′	100	
L.	90		L.	99	
	93	ham, milk, pumper-		94	beef
	96	nickel, tomato, peach		99	
	96			93	
D.	99		D.	97	
	98	beans, lamb, tomato,		99	potato, "very jumpy"
	97	peach, milk. Shaky		97	
	97	today		96	
July 26, 1942			*July 28, 1942*		
B.R.	77		B.R.	62	very jumpy, grapefruit
B.	100	corn flakes, sugar	B.	95	
30′	102		30′	82	
60′	93		60′	90	
90′	86	"shaky"	90′	106	major seizure, uncon-
					scious 5 min., milk
L.	90		Mid	102	
	95	cornflakes, sugar	A.M.	102	
	93			114	
	98			77	
D.	82	milk	Mid	103	pineapple
	85		P.M.	110	
	88			103	
	91			112	

on the patient's usual three-meal diet and for three days on a trial diet of selected, usually single, foods. The patient's chief complaint was idiopathic epilepsy (diagnosis confirmed at Rockland State Hospital, New York). Other symptoms, which disappeared after treatment, were abnormal tiredness, constipation, and canker sores. The operation was performed by Dr. Miscall, August 3, 1942. It is important to note that in the succeeding eight months, that is, in the period before the second pulse-dietary diagnosis was carried out, the number of seizures was "about the same as before the sympathectomy." As a therapeutic measure, then, the sympathectomy

was a complete failure, as it has been in so many other reported instances. Now, let us examine its efficiency as an antiallergic measure.

Table 6 shows the patient's record, made at the end of the eight-months period. Noteworthy are the generally lower level of the pulse on a large variety of foods; the characteristic constancy of the normal daily maximal pulse rate, 70–71; the reaction to cane sugar with carryover; and the internal evidence of the practical dependability of the patient's pulse counts. So we see that the seizures, continuing throughout the eight months following the

Table 6

C. W. Pulse Record after Sympathectomy

Time	*Pulse*	*Diet: symptoms*	*Time*	*Pulse*	*Diet: symptoms*
April 5, 1943			*April 7, 1943*		
B.R.	56		B.R.	67*	
B.	65	pineapple, milk	B.	79*	tomato, milk
30′	69		30′	69	
60′	64		60′	69	
90′	65		90′	68	
L.	62	egg, cheese, tomato,	L.	65	lettuce, egg, milk, to-
	68	milk, prunes		69	mato, cheese, pine-
	64			64	apple
	66			65	
D.	64	chicken,cabbage,	D.	64	lamb, milk, carrot,
	70	(lemon), carrot, milk		75*	peas, honey, apple
	67			68	
	67			69	
April 6, 1943			*April 8, 1943*		
B.R.	60		B.R.	60	
B.	70	tomato	B.	64	pineapple, milk
	64			66	
	65			68	
	66			65	
L.	61	egg, tomato, cheese,	L.	63	tomato, peas, milk,
	69	milk, pineapple,		65	apple
	71	prune		66	
	67			61	
Eve.	64	grapefruit, **sugar**	D.	64	lamb, tomato, beans,
	74			68	apple, honey, milk
	76			71	
	73			69	
	66				

* Carry-over from cane sugar.

operation, were due to the daily eating of three of her residual allergens: cereals, potato, and cane sugar. Her other residual allergens are fish, dill pickle, and cascara, each of which has caused a *grand mal* seizure.

In the succeeding four years, this young woman, after the usual secretarial course of instruction, has occupied a responsible position in a well-known business establishment. She has occasionally indulged liberally in forbidden sweets on a Friday evening, has regularly experienced the expected seizure on the following morning at home, has cleared her alimentary canal with

laxatives during the day, and has quite recovered in time for her Monday morning appointment. Epilepsy, with her, has become a purely experimental episode.

The antiallergic effect of interruption of sympathetic nerve-chain function has been dramatically illustrated in two cases with the single injection of procaine into a stellate ganglion. The injections were made by Dr. E. A. Rovenstine at Bellevue Hospital.

Patient E. C., a longtime sufferer from a marked destructive conjunctivitis, chronic rhinitis, and atopic dermatitis, had been found by two well-known allergists to be skin-sensitive to numerous inhalant allergens but not to any foods. With the pulse criterion, he was sensitive to so many foods that sympathectomy was advised. Dr. Miscall approved the suggestion of a preliminary procaine block of the stellate ganglion, which was performed October 4, 1946.

The pulse, previous to the block, had ranged as high as 92 on a succession of single foods and was usually above 81 (his normal maximum). Just before the injection, it stood at 84, and one hour later, at which time he took a quart of milk, it was at 83. Thirty minutes thereafter, it was 75, and it did not rise above 81 in the next 48 hours, excepting a little in the evening, probably on account of exposure to tobacco smoke to which he is very sensitive (pulse up to 104 while smoking).

The block broke at 48 hours, the pulse rising suddenly to 88 and remaining above normal until a second block was established. Under the protection of the blocks, it could be determined that at least sixteen foods could eaten without allergic reaction. With this information, both Dr. Miscall and the patient agreed to the operation. So also did Dr. Conrad Berens, in whose special care the patient had placed himself.

The information obtained with the pulse-dietary technique in the block of the stellate ganglion was useful not alone in permitting a preview of the permanent benefit to be expected from the sympathectomy. The tissue damage involved in the operation causes an irregular acceleration of the pulse that continues for several weeks, in which period, therefore, the interpretation of any changes in the pulse following a test meal might be undependable. This difficulty was marked and prolonged in the case of E. C., but he could evade it by simply limiting his diet to the sixteen foods (an ample diet) that had been found safe in the period of the blocks.

Patient B. C., for many years a sufferer from atopic eczema with an almost intolerable itching, had been referred to me by Dr. M. B. Sulzberger. With the pulse criterion, she was found sensitive to egg (vomiting and pulse of 90) and to the zinc ointment that she was using (pulse up to 96 in two tests before breakfast). Otherwise, no other allergens could be identified. The pulse constantly ranged above her normal maximum (80).

The injection of procaine (Rovenstine) was made at 12:20 P.M. There was a brief dizziness, and at 12:25 the pulse was 60, rising at 12:35 to 64. The itching ceased immediately after the injection and the patient's usual tenseness was replaced by a complete relaxation. In the succeeding 96 hours, the pulse remained between 64 and 80, excepting after a test with

lamb (88) and grapefruit (88). Both of these tests were followed by a brief recurrence of the itching. Under the protection of the block, 18 foods could be identified as nonallergenic.

Discussion

As we have seen, the pulse-dietary technique provides a dependable objective measure of the antiallergic effect of sympathectic ganglionectomy or procaine block. It must be emphasized that, in my joint study with Miscall, Rovenstine, and others, these procedures have been employed only in conditions that have been proved, through the pulse-dietary method alone, to be allergic. These have been hypertension, epilepsy, vertigo, psychoneurosis, gastrointestinal allergy, stammering with tic, migraine, irritability, destructive conjunctivitis, allergic eczema, and urticaria. Moreover, they have not been applied in the cases that have been easily solvable with the dietary regime but in those difficult cases that are found sensitive to too many important foods. In our experience, then, the operation, properly employed, supplements the dietary procedure, increasing the effectiveness of the latter to a high percentage of clinical success, depending somewhat on the intelligence, character, and economic circumstances of the patients.

It has not yet been known to abolish sensitivity to an inhaled allergen (dust, perfume, tobacco, cement, paint fumes, *etc.*).

Sympathectomy offers a smaller prospect of usefulness in subjects sensitive to only few foods, since the few sensitivities *could* be just those which would by chance not be abolished by the operation in the particular person. However, the "prognostic stellate block" can be profitably employed even in such cases, and the decision as to operation can be made according to the outcome.

Finally, it should be emphasized that, according to the results of my study of the antiallergic effect of sympathectomy, the operation should no longer be considered as a therapeutic measure for the relief of particular symptoms but almost always as a means of lessening the extent and severity of the food allergy that causes them and so facilitating its complete dietary control.

A Brief Critical Review of the Literature Concerning Sympathectomy and Sympathectic Procaine-Block

Having set forth the details of my own special use of these procedures, I can more readily discuss their different use by earlier experimenters.

Sympathectomy was employed as a therapeutic measure from the latter part of the 19th Century. It was applied locally for the relief of many symptoms, which at the time were not (and indeed still are not) generally believed to be due to the same cause (certainly not an allergic one, although some were conceived to be caused by some mysterious neurogenic "imbalance"). The list includes Raynaud's disease, thromboangiitis obliterans, asthma, cardiospasm, constipation, migraine, paroxysmal tachycardia, neuralgia, angina pectoris, essential hypertension, chronic arthritis, and epilepsy. Most of these have now been shown to be allergic, that is, they represent variously localized manifestations of a single, hereditary, constitutional disability.

The earlier experimenters proceeded according to their hypothesis that the symptoms were due to some local neurogenic abnormality ("imbalance of sympathetic and parasympathetic control") and thus to the logic that the ganglionectomy should be done close to the supposed source of the symptoms and with meticulous thoroughness. Thus, for migraine and facial neuralgia, the cervicodorsal ganglia are removed and the vertebral and carotid arteries may be stripped. For essential hypertension of supposedly renal origin, on the other hand, the favored operation is now removal of the upper lumbar ganglia and both celiac ganglia and even more extensive destruction.

I have called attention elsewhere[1] to the consensus of surgical observers that removal of lumbar and celiac ganglia was frequently followed by relief of headache and other symptoms, even when the hypertension persisted. This "paradox," as it is called by some operators, seems not to have disturbed the general assumption of a local action of sympathectomy. Unfortunately, also, the stony conservatism of some neurosurgeons has so blinded them to the clear significance of those reports that they still refuse the benefit of the conservative operation that I have described, even to the most desperate case of migraine.

We reach the conclusion, then, that the essential benefit of sympathectomy derives from its constitutional antiallergic effect and that the selection of the site of its performance should be determined not according to the locality of the chief symptom but according to general surgical principles.

In one case (E. C.) a left cervical ganglionectomy was done. Shortly thereafter, there was improvement in vision and in the conjunctivitis, but this was limited to the right eye. There was also a general clearing of the atopic dermatitis, but the left side of the face and left ear, the side of the operation, remained unimproved. This one experience is not conclusive, but it suggests a possible *unfavorable* local action of the operation in some instances.

For the present, the procedure of choice would seem to be the removal of two or three lumbar ganglia on one side only, wherever the chief food-allergic symptom may be located.

The ganglion block that has been used by Rovenstine as a valuable preliminary aid in the application of the antiallergic sympathectomy has been used for a similar purpose since 1925 by Mandel,[2] Swetlow,[3] White,[4] and Flothow.[5] At first, alcohol was recommended and, later, this was preceded by procaine. In a single experiment, we found that the injection of alcohol (at the second block in patient E. C.) caused a persistent moderate tachycardia which interfered with the interpretation of the pulse-dietary record.

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